IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

CEPHALON, INC. and CIMA LABS, INC., Plaintiffs, v. MYLAN PHARMACEUTICALS INC. and MYLAN INC., Defendants.	Civil Action No. 11-164-SLR

PLAINTIFFS' OPENING POST-TRIAL BRIEF ON INFRINGEMENT

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I. INTRODUCTION

- "[E]ffervescence has a larger effect on pK than other pH modifiers; pH modification and effervescence are not equivalent."

  (Mylan presentation reviewing fentanyl buccal data dated 3/1/12 (DTX 680 at MYLAN 518091).)

- "Fentora and our Buccal formulation use effervescent couple to take advantage of [the pH behavior of fentanyl]
  - CO_2 is created, dissolves in water (carbonic acid) - pH Decreases ([fentanyl increased] solubility)
  - CO_2 later released (to air or tissue), pH gradually increases ([fentanyl increased] permeability)"

  (Mylan presentation reviewing fentanyl buccal data dated 5/2/11 (PTX 75.7).)

- "Having this effervescent formulation at this level had a different performance than the non-effervescent dosage forms that we dosed. I'm not – that's the way the data says. It's the data. It's – it's what is revealed in all these testing. That's what it says."

  (Tammy Bartley, Mylan's lead formulator (deposed 4/10/12) (D.I. 148 at 392:6-11).)

Before trial of this matter, Mylan's scientists understood full well what the "data" in this case "says"—that the effervescent components in Mylan's generic fentanyl buccal tablets enhance absorption above and beyond other pH modifiers and above and beyond non-effervescent tablets, and that they do so through the dynamic pH mechanism described by Dr. Khankari at trial. Just as CIMA scientists learned through their work in Ireland, the Anesta dog study and the *in vitro* Absorption Systems study, Mylan scientists learned that effervescence has a striking effect on transmucosal absorption. Simply put, effervescence works, and works well.

These same Mylan scientists' failure to develop a bioequivalent "non-infringing," non-effervescent formulation ultimately led Mylan to copy Fentora®. The result of that calculated decision is that Mylan's generic fentanyl tablets infringe the patents-in-suit. As Mylan's "data" and the other evidence of record amply demonstrate, Mylan's tablets employ effervescence to increase absorption of fentanyl across the buccal mucosa, as claimed in the Khankari patents.

And because Mylan copied Fentora®, Mylan's tablets follow the specific recipe of the Moe patents that surprisingly achieves still further increased fentanyl absorption at lower doses.

Because Mylan can't change these facts, it seeks shelter in legal arguments that purport to apply the language of the asserted claims, but in reality twist that language beyond reason. For the Khankari patents, Mylan contorts the Court's claim construction to suggest that Cephalon must prove that effervescence improves absorption independent of any pH effect or pH modifier. But the Court's claim construction does not require that—it simply requires that the "amount" of effervescent agent that enhances absorption cannot include the "amount" of the pH modifier separately claimed. There is no prohibition on effervescence acting to affect pH or from acting synergistically with a pH modifier to achieve a dynamic pH effect. And, as Mylan itself recognized, effervescence plus a pH modifier has a "larger effect" than "other" pH modifiers. As to disintegration, none of the effervescence in Mylan's tablets is "required" for disintegration as the Court's construction provides. Mylan's tablets include the superdisintegrant sodium starch glycolate for that purpose, in an even greater amount (4%) than Fentora® (3%). Because of these separate superdisintegrants, effervescent and non-effervescent tablets disintegrate similarly when in the buccal cavity, as shown at trial. Effervescence is not "required" for disintegration.

On the Moe '158 patent, Mylan strangely contends that the sodium carbonate in its tablets—which it admits is the pH-adjusting substance claimed in the Moe '92,832 patent—cannot be the claimed pH adjusting substance because some of that carbonate might participate in an effervescent reaction. But all of that carbonate assuredly does not. The sodium carbonate in Mylan's tablets is a pH adjustor in the '158 patent, just as it is in the '92,832 patent.

The Court should reject Mylan's strained legal contortions and find what Mylan's

scientists already know—Mylan uses effervescence to enhance absorption and thus infringes the patents-in-suit. Judgment should be entered in Cephalon's favor, and Mylan should be permanently enjoined from the commercial manufacture, use, sale, offer for sale, and importation of its ANDA Products.

II. NATURE AND STAGE OF PROCEEDINGS

This case concerns four patents listed in the Orange Book as covering Fentora® brand fentanyl buccal tablets: U.S. Patent Nos. 6,200,604 (the "'604 patent") and 6,974,590 (the "'590 patent") (together, the "Khankari patents"; JTX-2; JTX-4); and 8,092,832 (the "'92,832 patent") and 8,119,158 (the "'158 patent") (together, the "Moe patents"; JTX-6; JTX-8).

On February 24, 2011, Cephalon sued Mylan for infringement of the Khankari patents, after having received notice from Mylan that it had filed an ANDA with a Paragraph IV certification seeking FDA approval of its 300 mcg generic fentanyl citrate buccal tablets before the Khankari patents expire (C.A. No. 11-164). (D.I. 138, ¶ I.4.) After Mylan notified Cephalon that Mylan had filed an amendment to its ANDA for additional strengths of the tablets (collectively "Mylan's ANDA Products" or "Mylan's tablets"), Cephalon filed a second complaint on the Khankari patents on November 9, 2011 (C.A. No. 11-1111). (D.I. 138, ¶ I.8.)[1]

On January 10 and February 21, 2012, respectively, the PTO issued the '92,832 and '158 patents. Thereafter, Cephalon sued Mylan for infringement of the '92,832 and '158 patents (C.A. Nos. 12-73 and 12-247). (D.I. 138, ¶¶ I.11, I.14.) The four actions are now consolidated. (D.I. 138, ¶ I.18; D.I. 49; D.I. 72; D.I. 86.) A bench trial was held from March 11 to 15, 2013. The trial addressed the remaining issues between the parties: infringement of claims 1, 2, 3, 11,

[1] Because Mylan amended its ANDA to include additional strengths, the 30-month stay as to those other strengths expires at a different, later time than for the 300 mcg strength. Cephalon will be prepared to discuss this issue on the telephone conference scheduled for June 19, 2013.

and 12 of the '604 patent and claims 1, 2, and 7 of the '590 patent; validity of claims 1, 3, 4, and 5 of the '92,832 patent; and infringement and validity of claims 1, 15, 17, 19, and 21 of the '158 patent. (D.I. 144.) Mylan had also contended the Khankari patents were invalid throughout the litigation, but dropped its counterclaim on the eve of trial. (D.I. 144.)[2]

III. SUMMARY OF ARGUMENT

The overwhelming trial evidence demonstrates that Mylan's ANDA Products literally infringe the asserted claims of the Khankari patents. Each limitation of the asserted claims is met, including the sole limitation that Mylan contends is not: "at least one effervescent agent in an amount sufficient to increase absorption." The citric acid and sodium bicarbonate in Mylan's ANDA Products—the precise components for effervescence identified in the fentanyl examples of the Khankari patents and that are also used in Fentora®—plainly meet the Court's construction of that term from the *Watson* case that the parties agreed applies here (D.I. 117):

> At least one compound that evolves gas by means of an effervescent reaction is present in an amount sufficient to increase the rate and/or extent of absorption of an orally administerable medicament across the oral mucosa. This amount is greater than that required for disintegration and does not include the pH-adjusting substance separately claimed.

The citric acid and sodium bicarbonate in Mylan's ANDA Products are effervescent agents because they participate in a reaction that evolves gas. They are also present in an "amount" greater than "required" for tablet disintegration. No "amount" of citric acid or sodium bicarbonate is "required" for tablet disintegration—as admitted in Mylan's ANDA, Mylan's tablets contain a superdisintegrant, sodium starch glycolate, for precisely that purpose. Nor does the "amount" of the effervescent agent need to include the pH adjustor in Mylan's tablets,

[2] In addition, Cephalon's complaint in C.A. No. 11-1111 also alleged infringement of two other patents issued to Dr. Moe, U.S. Patent Nos. 7,862,832 and 7,862,833. (D.I. 138, ¶ I.8.) Before trial, Cephalon informed the Court that it would not assert infringement of those patents against Mylan. (D.I. 144.)

sodium carbonate. Lastly, as Mylan's scientists understood before this trial, the effervescent agents in Mylan's tablets, as well as in Fentora®, enhance the rate and/or extent of absorption of fentanyl across the oral mucosa. These agents dramatically increase absorption over both non-effervescent formulations and formulations that employ only a pH adjustor, whether through the dynamic pH effect described by Dr. Khankari—*i.e.*, producing ideal pH conditions for both solubility and absorption—or through other mechanisms.

Mylan's ANDA Products also literally meet each and every limitation of the asserted claims of the Moe '158 patent. Mylan's ANDA Products contain a pH adjusting substance (sodium carbonate) that is not a component of the claimed effervescent material (citric acid and sodium bicarbonate). Mylan admitted that sodium carbonate is a pH adjusting substance under the Moe '92,832 patent, and its convoluted arguments to exclude that same pH adjusting substance from the scope of the '158 patent should not be credited by the Court.

IV. STATEMENT OF FACTS

A. Fentora® Rapidly Delivers Fentanyl to Treat Breakthrough Cancer Pain

In 2006, FDA approved Fentora® for the management of breakthrough pain in opioid-tolerant cancer patients. (D.I. 147 at 86:3-19, 87:19-88:7, 100:18-21; D.I. 151 at 1106:23-1107:3, 1269:13-17; PTX-237.) Mylan is the fourth of five generic companies to date that have sought FDA approval to sell generic versions of Fentora®. (C.A. Nos. 08-455, 08-330, 10-123, 11-164, 11-1152.) The others are Watson (enjoined), Barr (settled), Sandoz (case dismissed), and Impax (trial set for June 2013).

Many cancer patients suffer intense pain. They experience persistent or background pain that may be caused by cancerous tumors or as a side effect of therapy. (D.I. 147 at 68:11-69:10.) Doctors treat this persistent pain with around-the-clock opioid medication. (*Id.* at 69:22-70:12.)

Cancer patients additionally experience flares of very severe and intense pain called

breakthrough pain. (*Id.* at 68:11-69:21.) These flares generally persist for about an hour, but can last anywhere from a half-hour to two or more hours, and "break through" the around-the-clock medication patients receive to manage persistent pain. (*Id.* at 69:22-70:12, 71:8-72:1, 75:23-76:11; D.I. 151 at 1141:13-1143:9; PTX-361.)

The prevalence of breakthrough pain was first comprehensively studied in the early 1990s. (D.I. 147 at 70:13-72:1; PTX-242.) At that time, breakthrough pain treatment options were few: intravenous therapy in the hospital or short-acting oral opioids at home. (D.I. 147 at 72:2-14.) Unfortunately, the therapeutic effect of short-acting oral opioids did not adequately match the temporal characteristics of breakthrough pain. Because oral opioids are absorbed across the gastrointestinal tract, it takes time for them to exert a therapeutic effect. By the time that occurs, the pain episode may have already reached its peak. (*Id.* at 76:12-77:4.) Though not ideal, short-acting oral opioids were at least better than simply increasing around-the-clock opioid medication, which could cause sedation or severe side effects. (*Id.* at 74:10-75:22.)

In 1998, FDA approved the first oral transmucosal therapy specifically indicated for the treatment of breakthrough pain in opioid-tolerant cancer patients, Actiq®. (*Id.* at 73:4-10; DTX-586.) Actiq® was developed by Anesta Corp., a competitor company to CIMA. (D.I. 149 at 708:8-13.) The active pharmaceutical ingredient in Actiq®—a lozenge on a stick ("lollipop") formulation—is fentanyl, an exceedingly powerful opioid. (DTX-586; D.I. 147 at 73:4-10.) Fentanyl is fifty to one hundred times more potent than morphine, and can cause death if any substantial amount is absorbed, even through the skin. (D.I. 147 at 73:24-75:9; D.I. 150 at 914:22-24.) Because of this, fentanyl is delivered in microgram (mcg), not milligram (mg), quantities like other opioids. (D.I. 147 at 73:24-74:9; D.I. 150 at 914:22-915:22.) The largest dose of Actiq®, for example, is 1600 mcg, just 1.6 mg. (DTX-586 at 3.) Formulators use as

little fentanyl as needed to achieve a desired therapeutic benefit. (D.I. 147 at 74:10-75:22, 101:6-12.)

Actiq® offered an improvement in breakthrough pain therapy over short-acting oral opioids because its transmucosal delivery resulted in a faster onset of action. (*Id.* at 77:5-11, 79:6-12; D.I. 150 at 915:23-916:15.) But Actiq® had drawbacks. Substantial portions of the fentanyl were swallowed, defeating the purpose of transmucosal delivery. (DTX-586 at 8.) Moreover, as Dr. Blinderman explained, administering Actiq® required active manipulation, which is impractical for many cancer patients. (D.I. 147 at 79:20-83:15; PTX-472; DTX-586.) Actiq® also posed risks of diversion to drug addicts, as well as dental caries, and caused some patient users to experience social stigma. (D.I. 147 at 83:16-86:1.)

Approved in 2006, Fentora® achieves the clinical benefit of faster onset of pain relief than Actiq®, using a smaller amount of fentanyl per dose. (*Id.* at 147 at 86:3-19, 87:19-88:7, 91:16-92:25; D.I. 148 at 285:7-12; PTX-237.8-9; PTX-238; PTX-247.) Fentora® achieves these results by using the inventions claimed in the Khankari and Moe patents.

B. The Discovery of Effervescence to Increase Absorption Across the Oral Mucosa

The Khankari patents describe and claim the use of effervescence to increase absorption of drugs across the oral mucosa, in general, and fentanyl, in particular. (JTX-2; JTX-4; *see also* D.I. 147 at 184:12-187:15.) The oral mucosae are the mucous membranes lining the mouth, and include the buccal, sublingual, and gingival mucosae. (D.I. 147 at 77:5-78:6, 153:23-154:8.) The buccal mucosa is along the inside of the cheek; the sublingual mucosa is under the tongue; and the gingival mucosa is between the upper lip and gums. (*Id.* at 77:5-77:21, 154:4-8; D.I. 149 at 723:3-724:16.)

When a drug is administered by an oral transmucosal route, the drug is absorbed across

the oral mucosa and directly into the blood stream. (D.I. 147 at 154:9-19.) This is different than traditional oral administration where a dosage form is swallowed and the drug is absorbed across the gastrointestinal mucosa. (*See id.* at 150:17-21, 153:11-14, 156:11-17, 158:7-10.) Oral transmucosal administration can be beneficial for some drugs, both because the direct absorption can be faster, and because it avoids degradation of the drug by the liver—the so-called "first pass effect" explained by Dr. Khankari at trial. (*Id.* at 157:8-158:24; *see also* D.I. 149 at 723:10-22.)

Lipophilic drugs like fentanyl cross the oral mucosa to reach the bloodstream primarily by the "transcellular" pathway, as opposed to the "paracellular pathway." (D.I. 147 at 155:21-156:10.) In transcellular absorption, the drug travels through cell membrane walls, cell-by-cell, until reaching the bloodstream. (*Id.* at 154:23-155:20; D.I. 149 at 725:14-24.) In paracellular absorption, the drug travels between cells to reach the bloodstream. (D.I. 147 at 154:20-155:13; D.I. 149 at 725:14-24.)

Dr. Khankari began work on effervescence to enhance oral transmucosal absorption in roughly 1995, when he joined CIMA. (D.I. 147 at 148:17-18, 158:25-159:7.) At that time, CIMA served primarily as a contract manufacturer that made effervescent tablets for other companies. (*Id.* at 149:8-14, 227:13-25.) Those effervescent tablets were intended for oral administration—effervescence was used to rapidly disintegrate the tablet (in a matter of seconds) in the mouth, thus creating a slurry for ease of swallowing. (*Id.* at 150:17-151:18, 153:11-14.) In those tablets, the drug would be coated with materials to prevent transmucosal absorption. (*Id.* at 153:11-14; PTX-448 at abstract.)

At the same time it was marketing this technology—known as OraSolv®—CIMA was also trying to break into the drug delivery business, *i.e.*, the use of unconventional technologies or routes of administration to deliver drugs. (D.I. 147 at 148:15-23, 149:15-23.) To that end,

CIMA turned to Dr. Joseph Robinson, a professor at the University of Wisconsin and "a legend" in the drug formulation sciences, who served on CIMA's board of directors. (*Id.* at 158:25-159:19.) In 1995, Dr. Robinson had a graduate student, Jonathan Eichman, who was exploring the possibility of using effervescence to increase drug absorption across the gastrointestinal mucosa. (*Id.* at 158:25-160:12.) Mr. Eichman concluded from his investigation that bubbling carbon dioxide (CO_2) onto a gastrointestinal membrane improved paracellular drug absorption. (*Id.* at 160:13-162:2; PTX-18.1, .6.)

Sometime in 1995, Dr. Robinson brought this work to CIMA for evaluation. (D.I. 147 at 158:25-159:13.) Drs. Khankari and Robinson brainstormed how they might utilize carbon dioxide to improve oral mucosal absorption of a drug absorbed via the transcellular pathway—as stated, the primary absorption pathway in the oral mucosa. (*Id.* at 162:3-17.) Together, they theorized that the carbon dioxide gas produced by effervescence could increase oral transmucosal drug absorption via the transcellular route at least through its unique, dynamic effect on the pH of saliva. (*Id.* at 162:3-164:10, 191:18-192:8.)

Dr. Khankari described at trial this dynamic pH effect, just as the Mylan scientists would describe it years later. (*Id.* at 163:7-164:10, 165:9-167:12; DTX 680 at MYLAN 518094.) An effervescent reaction in the oral cavity first forms carbonic acid in saliva, which depresses the pH of saliva. (*Id.*; D.I. 147 at 164:8-17, 194:3-6.) Because it is a weak acid, carbonic acid breaks down into water and carbon dioxide, which leaves solution. (D.I. 147 at 163:20-23, 166:22-167:2.) As the carbonic acid breaks down, its concentration is reduced, and the salivary pH begins to rise. (*Id.* at 163:20-164:1, 164:18-20.) The effervescent reaction thus causes a dynamic change in the pH of saliva. (*Id.* at 164:8-10.)

This dynamic change in salivary pH is beneficial because it promotes both drug

dissolution and absorption, without compromising one in favor of the other. (*Id.* at 167:13-18.) By way of explanation, in order for a drug to be absorbed, it first must dissolve into solution. Acidic pH levels favor dissolution of weakly basic drugs like fentanyl. (*Id.* at 162:18-21, 164:21-165:1, 699:15-25; DTX-411 at 150-151.) When weakly basic drugs dissolve, they take on their "ionized" form. But ionized forms of drugs like fentanyl are not favored for transcellular absorption—rather, "unionized" forms are. In turn, basic pH levels favor the unionized form of weakly basic drugs. (D.I. 147 at 162:3-164:6, 165:2-8.) Accordingly, tension exists between the optimal pH conditions for drug dissolution and absorption: one is acidic and the other is basic. (*Id.* at 162:3-163:6.)

Part of the drug formulator's quandary, then, is that the pH conditions that promote dissolution are often the opposite of those that promote absorption. (*Id.*; *see also id.* at 164:16-165:6.) In order to convert a weakly basic drug from its dissolved, ionized form to its absorbable, unionized form, the formulator must somehow change from the dissolution-favoring lower pH to the absorption-favoring higher pH. (*Id.* at 165:6-8.) A formulation having a single, static pH cannot optimize the pH requirements for both drug dissolution and absorption. Dr. Khankari discovered that an effervescent formulation can provide a dynamic change in pH, facilitating dissolution and absorption. (*Id.* at 163:7-164:10, 165:9-167:12; D.I. 148 at 557:23-559:22.) Such a result—having first a pH that favors dissolution followed by a pH that favors absorption—is the "holy grail for pharmaceutical scientists." (D.I. 147 at 162:22-163:6.)

After Dr. Khankari identified pain medications, including fentanyl, as candidate drugs for the technology, formulation work began. (*Id.* at 167:19-171:24; PTX-21; PTX-20.) Dr. Khankari's team prepared a variety of formulations, with different ingredients and highly varied amounts of effervescence—from 2.1% to 87.3%. (D.I. 147 at 171:4-176:14; PTX-19.1; PTX-

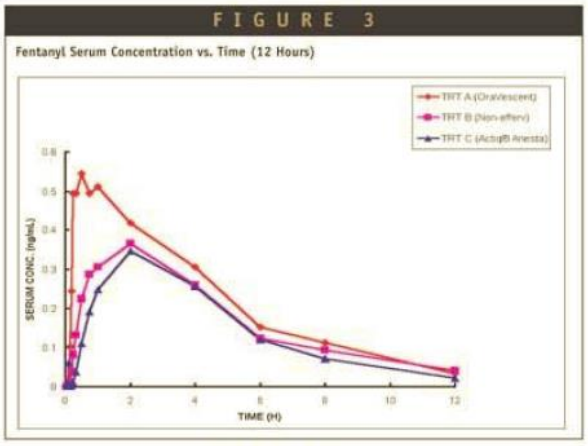
16.19.) This was done to understand the capabilities of the effervescent technology, which the team envisioned as a platform that could be used with numerous drugs. (D.I. 147 at 176:15-23.)

CIMA then commenced development work on two drug molecules suitable for commercialization: captopril and fentanyl. (*Id.* at 176:24-177:11.) That work led to a refinement to the CO_2-enhanced absorption technology: the addition of a pH adjusting substance to the formulation. (*Id.* at 177:12-20.) Adding a pH adjusting substance to the formulation, even beyond the effervescent components, offered the advantage of an additional pH boost for absorption (*i.e.*, further adjusting the pH to increase the amount of unionized drug form). (*Id.*) The pH adjusting substance could be an acid or a base, depending on the pH characteristics of the drug used in the platform technology. (*Id.* at 178:1-179:22; PTX-17.10, .14.) CIMA named the completed platform technology (*i.e.*, formulations containing both effervescent and additional pH-adjusting components) the OraVescent® technology. (D.I. 147 at 179:23-180:8.)

After settling on fentanyl as its lead commercial candidate, CIMA investigated its prototype OraVescent® fentanyl formulations *in vivo*, first in dogs. The dog study was run by competitor Anesta and, while Anesta scientists were unable to isolate non-pH related effects of effervescence, they confirmed Dr. Khankari's dynamic pH effect: the OraVescent® formulations produced higher fentanyl absorption than both non-effervescent formulations and buffered solutions of fentanyl at elevated pHs. (D.I. 149 at 587:5-591:6, 593:6-10, 705:3-22, 707:16-708:13; D.I. 150 at 956:1-958:12, 962:10-964:11; PTX-320.6, .20, .32-34.)

CIMA then studied its prototype effervescent formulation in humans. (D.I. 147 at 180:11-12.) In 2001, CIMA reported the results of the first clinical trial, which took place in Ireland. (*Id.* at 180:13-181:5; PTX-266A.) The Ireland study compared the Khankari prototype formulation utilizing the OraVescent® technology with both Actiq® and a buccal tablet lacking both

effervescent and pH adjusting components. (D.I. 147 at 181:13-25; PTX-266A.3-4; DTX-541 at CEP-FEN-00150997-98.) As depicted in the graph below, the OraVescent® Khankari prototype exhibited dramatically better pharmacokinetic ("PK") parameters than the other treatments, in both rate and extent of absorption. (PTX-266A.5.) The OraVescent® tablet (red) produced higher overall fentanyl absorption (AUC, a parameter relating to the extent of absorption), more quickly reached maximum fentanyl plasma concentration (T_{max}, a parameter relating to the rate of absorption), and achieved a higher maximum fentanyl plasma concentration (C_{max}, a parameter relating to the extent and rate of absorption) than both the non-effervescent fentanyl tablet (pink) and Actiq® (purple). (D.I. 147 at 182:1-183:21; D.I. 149 at 554:1-555:24, 616:17-25; 688:18-689:11; PTX-266A.5.)



Dr. Khankari and CIMA were ecstatic with these results. (D.I. 147 at 183:22-184:3.) Notably, and fatal to Mylan's non-infringement defense, the OraVescent® formulation and the non-effervescent formulation had "similar" disintegration times in the Ireland study. (D.I. 149 at 555:25-556:18; D.I. 150 at 938:6-939:22, 940:21-941:3; PTX-266A.3.) Both formulations contained 3% of the superdisintegrant crospovidone, and both disintegrated in roughly 10 minutes as measured by a disintegration test designed especially for buccal administration. (D.I. 150 at 938:6-940:9; DTX-541 at CEP-FEN00150997-998; PTX-266A.3.)

As to pH, the available data on the Ireland study indicate that the final pH values of the effervescent and non-effervescent formulations were the same, approximately 6.8 to 7.1. (D.I. 149 at 695:24-698:16; PTX-438.3.) And while Mylan's expert Dr. Weiner criticized the method of these pH tests, CIMA later changed its methodology for measuring pH and still confirmed Dr. Khankari's dynamic pH mechanism. (D.I. 150 at 892:3-24, 895:17-896:11, 899:16-903:7, 945:3-949:6; DTX-21 at CEP-FEN-009655581.) Indeed, years later, in 2006, CIMA measured the *in vitro* pH profile of effervescent fentanyl tablets, and found that the effervescent reaction resulted in a dynamic pH profile exactly as Drs. Robinson and Khankari had brainstormed all those years earlier. (D.I. 147 at 187:16-189:5; PTX-263.3; DTX-313.3; DTX-535 at CEP-FEN00466062.)

Ultimately Dr. Khankari and his co-inventors received both the '604 and '590 patents for their CO_2-enhanced oral transmucosal absorption inventions. (D.I. 147 at 184:12-187:15; JTX-2; JTX-4.) The '604 patent covers the platform technology and is not specific to any particular drug, while the '590 patent specifically relates to fentanyl. In their text, the Khankari patents explain the dynamic pH effect,[3] describing how effervescence and pH adjusting substances work synergistically to promote absorption across the oral mucosae:

> The pH [of] solutions in which an effervescent couple has dissolved is slightly acidic due to the evolution of carbon dioxide. The pH of the local environment, e.g., saliva in immediate contact with the tablet and any drug that may have dissolved from it, may be adjusted by incorporating in the tablet a pH adjusting substances which permit the relative portions of the ionized and unionized forms of the drug to be controlled. In this way, the present dosage forms can be optimized for each specific drug.

(D.I. 147 at 186:18-187:15; JTX-2 at 3:21-30.)

C. Commercial Development of OraVescent® Fentanyl Buccal Tablets Leads to

[3] The patents also refer to other possible mechanisms by which effervescence may act to increase absorption. (JTX-2 at 2:16-28, 4:32-35.)

Dr. Moe's Surprising Discovery of Further Enhanced Absorption Through the Use of Mannitol and Starch Glycolate

1. Dr. Moe Scaled Up Dr. Khankari's Prototype and Produced a 1080 mcg Effervescent Fentanyl Tablet Comparable to 1600 mcg Actiq®

With the Ireland study in hand, CIMA took the next steps toward commercializing its OraVescent® fentanyl buccal tablets: large-scale manufacture of the tablets and running additional clinical trials. (D.I. 147 at 184:4-11, 228:18-230:4.) This was an exciting project because it represented CIMA'S first full-fledged, independently developed product outside of the contract manufacturing space. (*Id.* at 227:13-228:17.)

Dr. Derek Moe, CIMA'S head of formulation, explained at trial how his team modified Dr. Khankari's prototype formulation to make it commercially viable. (*Id.* at 227:5-12, 228:18-24.) First, Dr. Moe's team had to make the prototype commercially manufacturable. (*Id.* at 229:1-235:12.) After about nine months of work representing approximately 7,000 man-hours of labor, Dr. Moe's team arrived at a scaled-up formulation they believed would succeed. (*Id.* at 235:2-12; *see also id.* at 237:15-238:1; PTX-259.20.) The revised, scaled-up formulation ("Khankari scaled-up formulation") contained micronized fentanyl citrate (as opposed to hand-milled fentanyl citrate), but largely used the same system the proved successful in the Ireland study: lactose monohydrate, sodium bicarbonate, citric acid, sodium carbonate, the superdisintegrant crospovidone, and magnesium stearate. (D.I. 147 at 236:8-237:14; PTX-444.12.)

Using the Ireland study as a baseline, CIMA also settled on a proposed dosing regimen for the Khankari scaled-up formulation. (D.I. 147 at 239:16-242:16.) Because Dr. Khankari's inventions allowed for an increased rate and extent of absorption over Actiq®, Dr. Moe and his team needed to determine what amount of fentanyl in the OraVescent® tablets would produce comparable absorption parameters to the various doses of Actiq®, which ranged from 200 mcg to 1600 mcg fentanyl. (D.I. 147 at 239:16-241:13; DTX-586 at 3.) Using computer modeling,

they predicted that a 1080 mcg fentanyl buccal tablet would be comparable to 1600 mcg Actiq®, a 32.5% fentanyl dose reduction. (D.I. 147 at 242:3-16; PTX-259.20.)

CIMA then conducted two clinical studies on the formulation, the 99-09 and 99-10 studies. (D.I. 147 at 242:17-245:23, 246:5-8; PTX-456A; PTX-317.) As hoped, these two studies demonstrated that a 1080 mcg dose of the Khankari scaled-up formulation provided comparable fentanyl blood levels to 1600 mcg Actiq®—further proof that effervescence was a superior delivery system. (D.I. 147 at 244:15-246:8; PTX-456A; PTX-317.) Understated as he might be, Dr. Moe expressed "joy" and "happiness" at these results. (D.I. 147 at 244:22-245:1.)

2. After Encountering Unexpected Fentanyl Degradation, Dr. Moe Created a New, More Stable Effervescent Formulation

But that joy quickly dissipated. Soon after receiving the clinical results on the Khankari scaled-up formulation, Dr. Moe and his team experienced an unexpected setback: the formulation was unstable. (*Id.* at 246:9-18; 247:7-251:25; PTX-259.24.) The fentanyl in the formulation "was actually converting into unknown other compounds" called degradants over time. (D.I. 147 at 247:7-248:3, 248:25-251:20.) These degradants essentially made the formulation unusable. (*Id.* at 248:4-18.)

So, it was back to the drawing board for Dr. Moe and his team. (*Id.* at 246:9-18.) The team set out to identify the source of the unexpected stability issues, working hard to look at the problem, and potential solutions, from several angles. (*Id.* at 252:8-17.) They ran forced degradation studies, excipient compatibility studies, and made dozens of additional prototype formulations. (*Id.* at 252:12-262:11; D.I. 148 at 341:4-21; PTX-324; PTX-259.10, .12.) In these studies they varied formulation ingredients, except those that Dr. Moe regarded as critical to the effervescent system: citric acid and sodium bicarbonate. (D.I. 147 at 261:12-17; PTX-259.12.)

Included among the variables tested by Dr. Moe's team were mannitol in place of lactose

monohydrate as a filler, and sodium starch glycolate ("SSG") in place of crospovidone as the superdisintegrant. (D.I. 147 at 258:23-260:10.) As Dr. Moe explained, CIMA had used these ingredients in other formulations, and they were convenient potential replacements. (*Id.*)

From the final round of accelerated stability testing on these prototype formulations, and after another eight to nine months and 7,000 man-hours of labor, Dr. Moe identified a new formulation as the best candidate to test in clinical trials. (D.I. 147 at 262:12-264:13; PTX-259.13; PTX-333.1.) The new formulation ("Moe formulation") employed mannitol and SSG as replacements for the lactose monohydrate and crospovidone, respectively. (D.I. 147 at 261:21-262:22, 264:21-265:11; PTX-333.1.)

But Dr. Moe had one last, important box to check before adopting the new formulation. He wanted to ensure that it did not produce a different PK profile than that of the Khankari scaled-up formulation because CIMA had planned to proceed into advanced clinical trials with the dosing regimen previously established with the Khankari scaled-up formulation. (D.I. 147 at 265:12-266:2; D.I. 148 at 276:22-277:7.) To that end, Dr. Moe's team performed disintegration tests on the Moe formulation to try to confirm that its PK profile would be similar to the PK profile of the Khankari scaled-up formulation. (D.I. 147 at 265:12-266:2; PTX-333.2.) *In vitro*, the Moe formulation tablets with SSG disintegrated more slowly than the Khankari scaled-up formulation tablets. (D.I. 147 at 266:3-18.) But the more predictive and important *in vivo* disintegration times between the two formulations were comparable. (*Id.* at 266:19-267:20.) And so Dr. Moe and his team expected that the PK profile of the Moe formulation containing SSG and mannitol would be comparable to the PK profile of the Khankari scaled-up formulation using lactose and crospovidone. (D.I. 147 at 267:21-268:6; D.I. 149 at 276:22-277:7.) With the approval of CIMA management, Dr. Moe's team then studied the Moe formulation in clinical

trials. (D.I. 147 at 263:12-18; PTX-333.)

3. Upon Testing, the Moe Formulation Unexpectedly Produced Superior Absorption Over the Khankari Formulation

And, again, the unexpected occurred. To Dr. Moe's surprise, in the first clinical study on the Moe formulation, the 99-11 study, the 1080 mcg Moe formulation tablet was ***not*** comparable to 1600 mcg Actiq®. Rather, an even ***lower*** dose—the 810 mcg strength Moe formulation—had a C_{max} comparable to 1600 mcg Actiq®. (D.I. 147 at 268:13-18, 270:2-24; D.I. 148 at 276:17-21; PTX-261.7.) To Dr. Moe's great shock, the Moe formulation was even better than the Khankari formulation. Specifically, in the 099-11 study, the 810 mcg Moe formulation tablet resulted in a C_{max} of 2,646.9 pg/mL, whereas the 1600 mcg Actiq® resulted in a 2,191.6 pg/mL. (D.I. 147 at 270:19-24; PTX-261.7.) But, in the 099-10 study, the 1080 mcg Khankari formulation resulted in a C_{max} of 2,570.951 pg/mL and the 1600 mcg Actiq® tablet resulted in a C_{max} of 2,264.145 pg/mL. (PTX-317.5.)

These results both surprised and frustrated Dr. Moe. (D.I. 147 at 268:13-269:3.) On the one hand, the results would allow for a further dose reduction in the amount of effervescent fentanyl that would be comparable to 1600 mcg Actiq®: from 1080 mcg of the Khankari formulation to roughly 800 mcg for the Moe formulation. But on the other hand, the results threw a wrench in CIMA'S plans to enter Phase III clinical trials with the previously chosen dosing regimen. (D.I. 147 at 268:19-269:3; D.I. 148 at 276:22-277:19.)

Phase III clinical trials are very expensive—for example, Dr. Moe testified that the Phase III clinical trials for Fentora® would cost CIMA on the order of $25 million. (D.I. 148 at 280:25-281:5.) Choosing the right high-end dose to test in those trials, the 1080 mcg or 810 mcg, was therefore not just a matter of academic interest. (D.I. 148 at 277:16-278:4.) If the 1080 mcg Moe formulation proved too strong, or the 810 mcg Moe formulation proved too weak, the

efficacy study would fail. (*Id.* at 277:24-278:4.) Debate ensued within CIMA about which dose to use, and CIMA even consulted with an outside pharmacokineticist, who was skeptical whether the lower dose should be used. (*Id.* at 278:5-280:9; PTX-131.)

Nonetheless, CIMA eventually adopted Dr. Moe's formulation containing SSG and mannitol and decided to adjust the doses of its fentanyl buccal tablets to change the top dose from 1080 mcg to 810 mcg before it moved into the multimillion dollar Phase III efficacy study. (D.I. 148 at 277:10-281:12; PTX-131.) That decision proved successful. A dose proportionality study (99-18) confirmed that choosing 810 mcg as the highest strength of the tablets was the right thing to do—810 mcg produced high enough C_{max} values to confirm a 50% dose reduction compared to Actiq® 1600 mcg. (PTX-367A; D.I. 148 at281:11-285:10.)

That study also demonstrated another peculiar aspect of the Moe formulation—that it is linear for doses of 810 mcg and below, meaning that a reduction in dose produces a correlating reduction in blood plasma levels—*i.e.*, half as much drug in the tablet will produce half as much drug in the blood. (D.I. 148 at 281:13-282:6, 284:14-285:3; PTX-367A.) But above 810 mcg, the formulation is not linear. (D.I. 148 at 285:4-6, 346:2-9; PTX-360.) Thus, the benefits of the Moe formulation can only be realized with doses less than about 800 mcg fentanyl. (D.I. 148 at 346:10-17.)

CIMA filed patents on the aspects of the Moe formulation that achieved the surprising PK results described above. (*Id.* at 287:2-16, 287:24-290:6.) Specifically, the patents relate to fentanyl formulations that include effervescent material, a pH adjusting substance, SSG, and mannitol with fentanyl doses less than about 800 mcg. The '158 patent succinctly explains the benefits of such formulations:

> It has been discovered that the use of effervescence and/or a pH adjusting substance, and most preferably both, can provide significant advantages

> particularly in terms of the amount of fentanyl that is required for dosing. It has also been found that certain disintegrants [i.e., SSG] and fillers [i.e., mannitol] in combination with at least one effervescent couple and at least one pH adjusting substance can provide even better, and very unexpected, results.

(JTX-6 at 8:65-9:5; JTX-8 at 9:16-25; D.I. 148 at 288:5-290:6.)

The Moe formulation ultimately became Fentora®, which is commercially available in the 800 mcg strength and lower strengths. (D.I. 148 at 280:20-281:12, 285:7-286:21; PTX-264.18.) Fentora® tablets are a commercial embodiment of all of the patents-in-suit. (D.I. 151 at 1208:5-8.) They use SSG and mannitol according to the Moe inventions with fentanyl doses below 800 mcg and employ effervescence to improve the delivery of fentanyl across the oral mucosa according to the Khankari inventions. (D.I. 148 at 285:16-288:7; PTX-264.18; PTX-237.7; PTX-259.14.) Indeed, the dynamic pH shift Mylan so derides is described on the FDA-approved Fentora® label (PTX 237.7):

> FENTORA® employs OraVescent® drug delivery technology, which generates a reaction that releases carbon dioxide when the tablet comes in contact with saliva. It is believed that transient pH changes accompanying the reaction may optimize dissolution (at a lower pH) and membrane permeation (at a higher pH) of fentanyl through the buccal mucosa.

As even Mylan's expert Dr. Weiner had to admit, drug labels must be accurate under the law and inaccuracies can be severely punished because both patients and doctors rely on these labels. (D.I. 150 at 921:9-18, 922:5-925:10.) These statements are not "marketing," as Mylan would have it; they are the science of Fentora®—science that Mylan formulators learned first-hand for themselves when they developed Mylan's proposed generic version of Fentora®.

D. Mylan's Fentanyl Citrate Buccal Tablets and Their Development Demonstrate that Effervescence Increases Fentanyl Absorption Across the Oral Mucosa

1. Mylan's ANDA Products Are a Virtual Copy of Fentora®

Mylan's ANDA Products include 100, 200, 300, 400, 600, and 800 mcg fentanyl citrate

buccal tablets. (PTX-292.1-02; PTX-188.1; PTX-293.) Each strength has identical ingredients: fentanyl citrate, sodium bicarbonate, sodium carbonate, citric acid, mannitol, SSG, silicon dioxide, and magnesium stearate. (PTX-188.1; PTX-292.1-2; PTX-293.) The strengths differ only with respect to the amounts of fentanyl citrate and mannitol, and the 100 mcg tablet is also 50% smaller. (PTX-188.1; PTX-292.1-02; PTX-293.)

Mylan's ANDA Products are nearly identical to Fentora®. Fentora® tablets contain the same ingredients, except silicon dioxide, and have the same strengths as Mylan's ANDA Products. (PTX-188.1-02; PTX-292.4; PTX-264.18.) Both Fentora® and Mylan's ANDA Products contain the same amount of sodium bicarbonate (21%) and citric acid (15%) by weight. Fentora® and Mylan's ANDA Products also both contain 10% sodium carbonate by weight. (PTX-188.1; PTX-264.18.) Both Fentora® tablets and Mylan's ANDA Products also contain around 50% mannitol by weight. (PTX-188.1; PTX-264.18.)

Fentora® and Mylan's ANDA Products also contain the identical superdisintegrant, SSG, though Mylan has added even more of the ingredient to its products: Fentora® contains 3% SSG by weight, whereas Mylan's ANDA Products contain 4% SSG by weight. (PTX-188.1; PTX-264.18.) Notably, Mylan's ANDA describes SSG as the disintegrant in its formulation. (PTX-188.1.) It does not identify effervescence as a disintegrant anywhere, stating instead that effervescence allows for rapid dissolution (PTX-188.3), just as Dr. Khankari's dynamic pH theory predicts.

As to the effervescence and pH adjusting components, Mylan's ANDA identifies the citric acid and both carbonates, sodium bicarbonate and sodium carbonate, as effervescent components, but is silent on the use of sodium carbonate as a pH adjustor. (PTX-188.1.) However, upon filing its ANDA with the FDA, Mylan originally sought a label that incorporated

the dynamic pH language from the Fentora® label:

> Fentanyl citrate buccal tablets employ the OraVescent®* drug delivery technology, which generates a reaction that releases carbon dioxide when the tablet comes in contact with saliva. It is believed that transient pH changes accompanying the reaction may optimize dissolution (at a lower pH) and membrane permeation (at a higher pH) of fentanyl through the buccal mucosa.

(PTX-251.2; D.I. 150 at 930:18-931:5.) As Dr. Weiner admitted at trial, only after a year of this litigation did Mylan suddenly change tack, and seek to delete that language from its label. (PTX-202.22; D.I. 150 at 931:6-934:14.)

2. Mylan's Star Formulators Failed To Make a Non-Effervescent Fentanyl Buccal Tablet That Was Bioequivalent to Fentora®

While containing mountains of detail required by FDA regulations, Mylan's ANDA devotes all of three sentences to alternatives to effervescence that Mylan tried in its development effort. (PTX-188.3.) But as is true generally, and is especially true here, actions speak louder than words. It is undisputed that the key limitation of Dr. Khankari's patents is the use of effervescence to improve absorption. Mylan had a substantial motivation to design a formulation that was bioequivalent to Fentora® without using effervescence. In fact, this Court concluded that Watson had done just that, although Watson was forced to use another patented Cephalon technology (a solid solution) to achieve bioequivalence to Fentora®. The Federal Circuit affirmed both of those infringement determinations. *Cephalon, Inc. v. Watson Pharms., Inc.*, 769 F. Supp. 2d 729 (D. Del. 2011), *rev'd on other grounds*, 707 F.3d 1330 (Fed. Cir. 2013); *Cephalon, Inc. v. Watson Pharms., Inc.*, 769 F. Supp. 2d 761 (D. Del. 2011), *aff'd* 446 Fed. App'x 306 (Fed. Cir. 2011).

Thus, although ultimately Mylan chose to copy the key components of Cephalon's Fentora® tablets, it did not initially set out to do so. Mylan chose that course only after its attempts to design-around the Khankari patents by making a non-effervescent formulation failed

to yield a bioequivalent product.

When Mylan initiated its fentanyl buccal tablet project in 2008, Mylan's then Vice President of Product Development, Dr. David Wargo, assigned the project to formulators Dr. John Twist and Tammy Bartley. (D.I. 148 at 396:1-3, 451:18-22.) Those individuals were among Mylan's most talented and experienced formulators. Both had 20 years' experience in formulations. (*Id.* at 383:25-384:2, 398:8-23.) Both were assigned to a special development group that handled first-to-file and various complex projects, known as the "First to File" team. (*Id.* at 397:1-398:23, 412:11-14, 513:19-514:12.) Dr. Wargo assigned the fentanyl buccal tablet project to the Twist/Bartley "First to File" team because Mylan hoped to file the first ANDA for generic Fentora®. (*Id.* at 396:4-25.) And while any formulation effort has challenges, Mylan had talented formulators who had solved difficult problems in the past. (*Id.* at 397:22-398:2.)

At project inception, Mylan's formulators reviewed the patents then listed in the Orange Book for Fentora®. (*Id.* at 398:24-399:11, 401:15-402:23; PTX-38 at MYLAN 157539-40.) Knowing that Fentora® contained effervescent agents and, seeking, among other things, to avoid infringement of Cephalon's patents, Mylan adopted the strategy of developing a non-effervescent formulation that used pH modifiers to reach a target pH of 7-7.5 to achieve bioequivalence—*i.e.*, using pH modification alone to try to achieve bioequivalence. (D.I. 148 at 402:13-404:17; PTX-46.6.) Mylan then made and tested in humans three different non-effervescent formulations with this approach. (D.I. 148 at 404:18-405:17.)

The first non-effervescent formulation, lot 1000306, included ascorbic acid and magnesium oxide as pH modifiers, micronized fentanyl and 5% of the superdisintegrant SSG, as well as other ingredients. (*Id.* at 405:10-407:5, 417:13-20, 425:24-426:1, 465:12-17; PTX-43.2; DTX-755 at MYLAN 479068.) But when tested in humans, the maximum blood concentration

of fentanyl observed from formulation 1000306 (C_{peak} or C_{max}) was only about half of that observed with Fentora®. (D.I. 148 at 407:6-409:6, 466:25-467:17; PTX-44.1; *see also* DTX-27; PTX-95.3 ("First BE Study Failed- Little or no Buccal absorption observed".) Formulation 1000306 also took nearly twice as long to reach this maximum concentration (T_{peak} or T_{max}) as Fentora®. (D.I. 148 at 409:7-411:18; PTX-44.1.) Traditional pH modifiers alone had failed.

This failure meant that Mylan lost the first-to-file race. (D.I. 148 at 414:17-415:4; PTX-95.3.) But based on this result, Dr. Twist thought it "imperative" for Mylan to "match the innovator with respect to pH-time profile as closely as possible." (D.I. 148 at 412:21-413:15; PTX-96.1.) Accordingly, he and his team made two more non-effervescent formulations (lots 1000367 and 1000368). (D.I. 148 at 413:16-19.) In these formulations, Mylan changed the pH modifiers from ascorbic acid and magnesium oxide to monobasic potassium phosphate and dibasic sodium phosphate. (*Id.* at 416:3-419:9, 467:18-25, 471:1-472:11; PTX-48.4; PTX-49.4.) But again the lots used micronized fentanyl, as well as 5% of the superdisintegrant SSG—indeed, accordingly to Ms. Bartley, they were based on orally disintegrating tablet (ODT) formulations that typically rapidly disintegrate. (D.I. 148 at 413:16-416:2, 417:2-20, 418:18-22, 425:24-426:2; PTX-48.4; PTX-49.4; PTX-95.3.)

Again, however, the non-effervescent formulations failed. In biostudies, lots 1000367 and 1000368 only reached 65-70% of Fentora®'s C_{peak}. (D.I. 148 at 420:4-421:14, 472:12-473:7; PTX-50.1.) These formulations also again had poorer times to maximum concentration than Fentora®. (PTX-50.1.) Once more, pH modification alone had failed. (D.I. 148 at 423:4-15, 472:18-473:7; D.I. 149 at 564:8-565:23; PTX-75.4; PTX-64.1 ("The non-effervescent formulations (all 400 mcg) did not show measureable buccal absorption when dosed against Fentora 400 mcg tablets.").)

3. Mylan's Formulators Turn to Effervescence to Achieve Bioequivalence to Fentora

After these three failed attempts to create a bioequivalent non-effervescent formulation, Mylan decided to switch to effervescent formulations in hopes of increasing fentanyl absorption. (D.I. 148 at 423:16-21; D.I. 149 at 565:18-23.) This decision could not have been an easy one, because if Mylan been able to achieve a bioequivalent product without using effervescence, that's "absolutely" the approach Mylan would have taken. (D.I. 148 at 516:5-8.)

In its first two effervescent formulations, lots 1000489 and 1000490, Mylan added sodium bicarbonate and citric acid as effervescent agents and continued to use micronized fentanyl and the superdisintegrant SSG. (PTX-56.5; PTX-57.5; D.I. 148 at 423:19-24, 425:3-23, 426:2-10.) Mylan also used sodium carbonate in these lots, describing it as part of the effervescent system. (PTX-56.5; PTX-57.5; D.I. 148 at 425:3-23, 431:3-8.)

In testing these effervescent formulations in humans, Mylan learned what CIMA had years before it: effervescence works very well to enhance transmucosal absorption—as it turned out for Mylan initially, too well. In contrast to its non-effervescent formulations, which produced PK values that were too low to be bioequivalent to Fentora®, Mylan's first two effervescent formulations overshot Fentora®, resulting in PK values that were too *high* to establish bioequivalence. (D.I. 148 at 426:11-429:5, 568:4-8; PTX-55; PTX-75.4.) Thus, to achieve bioequivalence to Fentora®, Mylan would now have to lower the bioavailability of its effervescent formulation—the opposite problem than Mylan initially faced. (D.I. 148 at 428:17-429:5.)

In order to get an approvable product, Mylan thus had to ratchet down the fentanyl blood levels of its effervescent formulations. Mylan considered two strategies: (1) increase the particle size of the fentanyl to make it less easily absorbed; or (2) decrease the amount of

effervescent couple to reduce the bioavailability of its effervescent formulations. (*Id.* at 429:6-19, 430:19-431:8; PTX-103.12.) Mylan chose to take the former approach and, after increasing the particle size of fentanyl, arrived at a bioequivalent formulation, lot 1000544, which became the formulation of Mylan's ANDA Products. (D.I. 148 at 434:6-17; D.I. 149 at 568:9-569:20; PTX-75.4.)

4. Mylan's Development Efforts Further Show That the Superdisintegrant Sodium Starch Glycolate Is Used to Disintegrate Its Tablets

In addition to testing the absorption of fentanyl in its biostudies, Mylan also studied the disintegration times of its non-effervescent formulations as compared to Fentora®, or, at least proxies for disintegration—*i.e.*, when tablet remnants, if any, were swallowed. And just as CIMA had learned in Ireland, non-effervescent formulations that include a superdisintegrant disintegrate similarly *in vivo* to effervescent formulations.

The superdisintegrant chosen by Mylan, SSG, is the same one used in Fentora®. As Ms. Bartley testified, SSG is used in orally disintegrating tablets, which will disintegrate in under 30 seconds. (D.I. 148 at 384:18-386:5.) Dr. Wargo agreed. (*Id.* at 415:8-416:2.) Each of Mylan's non-effervescent lots (1000306, 1000367, and 1000368) contained SSG at a concentration of 5%. (PTX-75.2, PTX-115.3; PTX-43.2; PTX-48.4; PTX-49.4; D.I. 148 at 417:7-20, 418:18-22; D.I. 149 at 563:20-564:7, 572:2-13.) In the 30-minute time allowed for in Mylan's biostudies, each of these formulations disintegrated similarly to Fentora®. Tablets from Mylan's first non-effervescent formulation, lot 1000306, disintegrated in about 27 minutes compared to about 24 minutes for Fentora®. (PTX-102.14, .18; DTX-680 at MYLAN 518160; DTX-27 at MYLAN 487574; D.I. 148 at 499:7-500:21, 501:4-502:11.) Likewise, the *in vivo* disintegration data for the 7 subjects who completed the clinical study for Mylan's next two non-effervescent formulations, lots 1000367 and 1000368, is also similar to Fentora®. (D.I. 149 at 573:21-

576:20; PTX-115.74.) For the Fentora® patients, 5 of 7 of the patients had tablet remnants at the 30-minute mark, while for the lot 1000367 and 1000368 patients, 7 of 7 patients had tablet remnants. (D.I. 149 at 576:10-20.)

As explained by Dr. Illum, none of these are significant differences, and the *in vivo* disintegration times were all comparable. (*Id.* at 574:21-575:15, 576:10-20.) Effervescence was not "required" to disintegrate any of Mylan's non-effervescent tablets. Indeed, even Dr. Wargo and Dr. Weiner had to admit that there was no disintegration problem with Mylan's first non-effervescent formulation, lot 1000306. (D.I. 148 at 499:14-502:1; D.I. 150 at 980:6-25; DTX-27 at MYLAN 487574; PTX-102.18.) And while claiming at trial that the lots 1000367 and 1000368 suffered from disintegration problems documented nowhere in writing,[4] both before trial and during trial, Dr. Wargo identified pH modification—not disintegration—as the primary purpose of the effervescent components in Mylan's tablets. (D.I. 148 at 448:14-449:7.)

None of this is any surprise. Each formulation contained similar amounts of the superdisintegrant SSG. And Fentora®'s labeling—as well as Mylan's proposed labeling—says that tablet remnants are likely to remain after 30 minutes, despite the use of effervescence. (PTX-237.16; D.I. 147 at 98:15-18, 112:14-24; D.I. 148 at 495:9-23; PTX-202.44.) This is the case because Fentora®, just like Mylan's formulations, contains insoluble excipients that will never go into solution, including SSG (Fentora® and Mylan), magnesium stearate (Fentora® and Mylan), and colloidal silicon dioxide (Mylan). (D.I. 148 at 493:11-22; PTX-188.1; PTX-264.18.) Accordingly, there will always be remnants to swallow. (PTX-237.16; PTX-202.44;

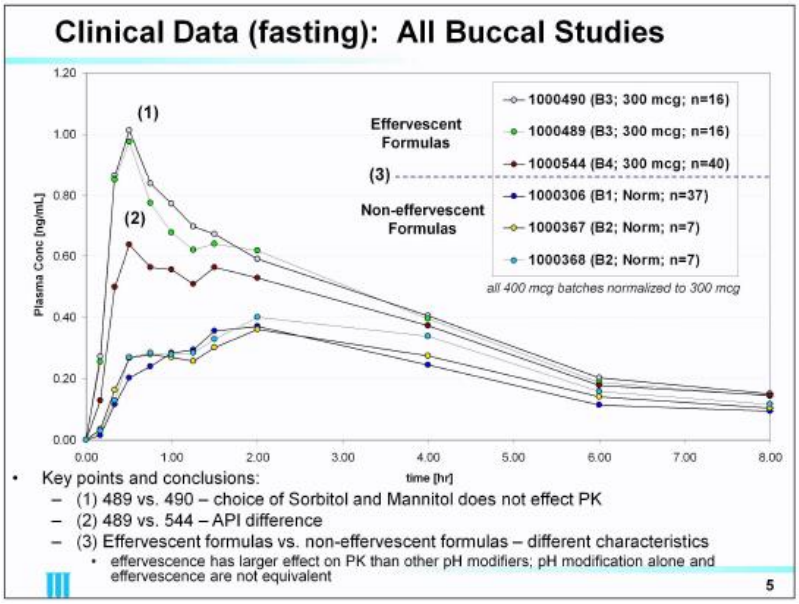
[4] While Dr. Wargo presented *in vitro* screen tests purporting to support this claim, nowhere do Mylan's documents actually say that disintegration was a problem. Indeed, as was plain at trial, and as Dr. Wargo admitted, effervescence was incorporated to take advantage of the dynamic pH effect invented by Dr. Khankari and Dr. Robinson.

D.I. 147 at 112:14-24; D.I. 148 at 495:9-23.) The superdisintegrant SSG, which Ms. Bartley testified she uses to disintegrate tablets in under 30 seconds, works just fine in effervescent fentanyl formulations.

5. Before Trial of this Matter, Mylan Agreed that Effervescence Improves Absorption Through a Dynamic pH Mechanism

While not disclosing all the above work to the FDA in its ANDA, Mylan presented it extensively internally in the hopes of using it to develop a version of a different generic fentanyl product, Abstral®, a sublingual fentanyl product made by Orexo. (PTX-64.)

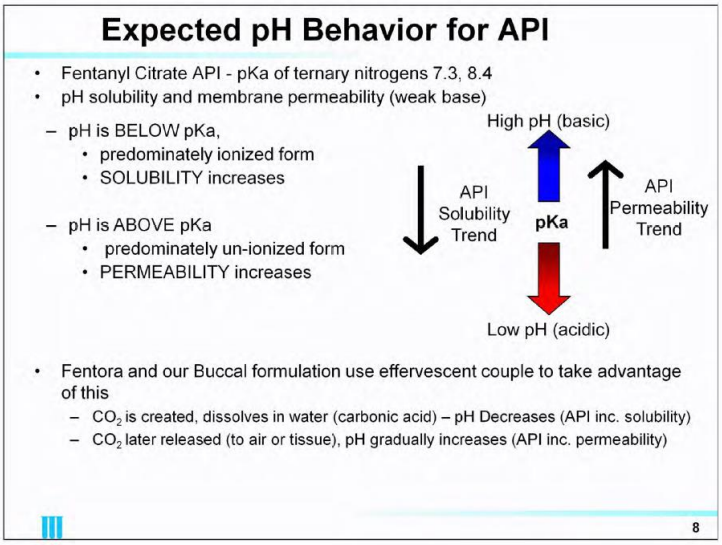
In May 2011, Mylan formulator Dr. Daniel Kuntz gave a presentation to Dr. Wargo summarizing Mylan's non-effervescent and effervescent fentanyl buccal tablet formulations for purposes of the Abstral® project. (D.I. 148 at 438:14-439:12; PTX-75.) Dr. Kuntz concluded that all three of Mylan's non-effervescent formulations "show similar PK profile/behavior." (PTX-75.2.) However, Dr. Kuntz concluded as a "key point" that Mylan's effervescent formulations have "***different*** characteristics" than Mylan's non-effervescent formulations. (D.I. 148 at 440:24-443:5 (emphasis added); PTX-75.4; *see also* PTX-115.5; DTX-680 at MYLAN 518091.) Those differences are depicted in one of Dr. Kuntz's slides, wherein the bottom three PK curves correspond to Mylan's non-effervescent formulations, the top two PK curves correspond to Mylan's initial effervescent formulations, and the middle PK curve corresponds to Mylan's final effervescent formulation that uses a larger drug particle size and that is bioequivalent to Fentora®—the "Goldilocks" formulation described by both sides at trial. (D.I. 148 at 441:19-442:13; D.I. 149 at 564:22-565:23, 568:4-8.)



(DTX-680 at MYLAN 518091; *see also* PTX-75.4).

As shown in Dr. Kuntz's figure, all three effervescent formulations achieve a higher C_{max} and reach that C_{max} faster than the non-effervescent formulations. Dr. Kuntz concluded from this that "effervescence has [a] larger effect on PK than other pH modifiers; pH modification alone and effervescence are not equivalent." (D.I. 148 at 443:19-445:2; DTX-680 at MYLAN 518091; PTX-75.4; PTX-115.5) Notably, he said nothing about effervescence and alleged disintegration improvements in this slide, as Dr. Weiner admitted. (D.I. 150 at 984:1-17; DTX-680 at MYLAN 518091; PTX-75.4; PTX-115.5.)

Dr. Kuntz then gave another presentation dated March 1, 2012 on the generic Abstral® work in progress. (D.I. 148 at 439:10-12; DTX-680; PTX-115.) In that presentation he repeated the slides given above, as well as others—*i.e.*, even after a year and a half of this litigation, he re-affirmed Mylan's conclusions. One of those slides described in detail the dynamic pH effect invented by Dr. Khankari, concluding that: "Fentora and our Buccal formulation use effervescent couple to take advantage of this [pH-dependent behavior]." (D.I. 148 at 489:12-490:6; DTX-680 at MYLAN 518094.)



Mylan's non-infringement claims, in the face of Dr. Kuntz's conclusions on these slides, are truly remarkable. But, then, Dr. Kuntz gave his presentations at times (May, 2011 and March, 2012) when the Khankari patents stood invalidated for lack of enablement[5]—he had nothing to fear about appropriating Cephalon's hard-earned technology, whether it be for the buccal tablets that are the subject of this case, or, potentially, for a generic version of a different company's product. And while Mylan now claims that all of this is essentially hokum, it has always known otherwise. About a year into Mylan's generic Fentora® project, in February, 2009—*i.e.*, before the Khankari patents stood invalidated—formulator Tammy Bartley prepared a presentation on the project's status and formulation approach, which, at that time, was to make non-effervescent ("design around") formulations. (D.I. 148 at 389:16-390:12, 454:17-456:3; DTX-27; PTX-46.) In this presentation, she described how Fentora® tablets use effervescence to cause a decrease in pH upon formation of carbonic acid and then a subsequent rise in pH as carbon dioxide is released from saliva in order to enhance absorption. (D.I. 148 at 389:16-

[5] This Court invalidated the Khankari patents on March 11, 2011, in the same ruling it held the patents not infringed by Watson. *Cephalon, Inc. v. Watson Pharms., Inc.*, 769 F. Supp. 2d. 729 (D. Del. 2011). As noted, the Federal Circuit affirmed the Court's non-infringement findings, but reversed on invalidity. *Watson*, 707 F.3d 1330.

390:12, 488:9-489:9; DTX-27 at MYLAN 487571.) This is the same mechanism that Dr. Kuntz articulated years later, and to which Ms. Bartley testified under oath. (D.I. 148 at 391:8-22 ("As the CO2 is liberated from the media, the pH will increase.").) As she said, perhaps more eloquently than anyone else at trial, "the data" "says" effervescence works. (*Id.* at 392:3-11.) "[I]t's what is revealed in all these testing." (*Id.* at 392:10-11.) Mylan infringes the patents-in-suit, and its scientists know it.

V. ARGUMENT

A. Legal Standards for Infringement

Because this is a Hatch-Waxman case, the Court's task on infringement is to determine whether Mylan's accused ANDA Products will infringe the Khankari and Moe patents, if those products are approved and sold. *Glaxo, Inc. v. Novopharm, Ltd.*, 110 F.3d 1562, 1569-70 (Fed. Cir. 1997). In this case, Cephalon alleges that the sale of Mylan's ANDA products will directly infringe the Moe patents, and indirectly infringe both the Khankari and Moe patents under the doctrines of induced and/or contributory infringement. Under each theory, Cephalon must prove infringement by a preponderance of the evidence. *SRI Int'l v. Matsushita Elec. Corp. of Am.*, 775 F.2d 1107, 1123 (Fed. Cir. 1985) (en banc). "A patentee may prove infringement by 'any method of analysis that is probative of the fact of infringement, and circumstantial evidence may be sufficient.'" *Martek Bioscis. Corp. v. Nutrinova, Inc.*, 579 F.3d 1363, 1372 (Fed. Cir. 2009).

Cephalon only asserts literal infringement in this case. To prove direct infringement of a composition claim, like the asserted claims in the Moe patents, Cephalon must show that those claims (as construed) read on Mylan's ANDA Products literally—*i.e.*, each element is literally met by Mylan's product. *See ActiveVideo Networks, Inc. v. Verizon Commc'ns, Inc.*, 694 F.3d 1312, 1319 (Fed. Cir. 2012).

To prevail on its induced infringement claim, Cephalon must prove, by a preponderance

of the evidence, that: a) Mylan knew of the Khankari or Moe patents; and b) Mylan will induce patients to perform the steps of the methods claimed in the Khankari patents, or use the compositions claimed in the Moe patents, and intend for them to do so. 35 U.S.C. § 271(b); *see AstraZeneca LP v. Apotex, Inc.*, 633 F.3d 1042, 1056-60 (Fed. Cir. 2010). A proposed drug label that instructs users to perform a patented method provides evidence of an affirmative intent to induce infringement of the patented method. *Id.* at 1058-61.

For contributory infringement of the Khankari patents, Cephalon must prove, by a preponderance of the evidence, that: a) Mylan knew of the Khankari or Moe patents; b) there will be direct infringement; c) Mylan's ANDA Products are non-staple articles of commerce with no substantial non-infringing uses; and d) Mylan's ANDA Products are a material part of the invention. *i4i Ltd. P'ship v. Microsoft Corp.*, 598 F.3d 831, 850-51 (Fed. Cir. 2010), *aff'd* 131 S. Ct. 2238 (2011); *Eli Lilly and Co. v. Actavis Elizabeth LLC*, 435 Fed. App'x 917, 927 (Fed. Cir. 2011) (non-prec.) (generic defendants liable for contributory infringement where FDA-authorized use was patented because "defendants are restricted from selling a federally regulated drug for unapproved uses").

B. Mylan's ANDA Products Meet the Only Disputed Element of the Khankari Patents: "At Least One [Saliva Activated] Effervescent Agent In An Amount Sufficient To Increase Absorption . . . Across the Oral Mucosa"

1. What Is—and Is Not—Required by the Court's Claim Construction from *Watson* of the Disputed "Effervescent Agent" Term

The only dispute on infringement of the Khankari patents turns on whether Mylan's ANDA Products contain "at least one [saliva activated] effervescent agent in an amount sufficient to increase absorption" of a drug across the oral mucosa. (D.I. 150 at 789:12-22, 792:7-15, 906:6-908:14.) By agreement of the parties, and consistent with this Court's construction in the *Watson* litigation, that claim element has the following meaning:

> At least one compound that evolves gas by means of an effervescent reaction [that] is present in an amount sufficient to increase the rate and/or extent of absorption of an orally administerable medicament across the oral mucosa. This amount is greater than that required for disintegration and does not include the pH-adjusting substance separately claimed.

D.I. 117 at 2; *Watson*, 769 F. Supp. 2d at 743.

Before comparing Mylan's ANDA Products to the agreed claim construction, it is important to make clear what the construction actually requires and, given Mylan's arguments, does not require. The first requirement is that Mylan's tablets must contain "at least one compound that evolves gas by means of an effervescent reaction" to infringe. A showing of "effervescence (as compared to a reaction of a different nature) is required." *Watson*, 769 F. Supp. 2d at 745. As described in the Khankari patents, effervescent agents "evolve gas by means of a chemical reaction which takes place upon exposure of the effervescent agent (an effervescent couple) to water and/or to saliva in the mouth," and most often results from the reaction of a soluble acid source and a source of carbon dioxide. (JTX-2 at 2:41-50; JTX-4 at 2:44-53.) Thus, Cephalon must demonstrate by a preponderance of the evidence that at least one compound in Mylan's ANDA Products participates in this effervescent reaction and evolves gas.

The second requirement is that the effervescent agent(s) in Mylan's tablets must be present "in an amount sufficient to increase the rate and/or extent of absorption of an orally administerable medicament across the oral mucosa." That is, the rate and/or extent of drug absorption following oral transmucosal administration of an effervescent formulation must be increased compared to a non-effervescent formulation. The construction does not rule out that another substance may also contribute in part to this increased absorption in a synergistic manner, but rather that the effervescence enhances absorption, whether by itself or with another component. Nor does this construction require any proof of the mechanism by which

effervescence increases absorption. While Cephalon strongly believes that effervescence increases absorption through a dynamic pH mechanism —something with which Mylan's scientists all agreed before trial—technically, Cephalon is not required to prove this mechanism, as Mylan's own expert Dr. Weiner conceded. (D.I. 150 at 908:16-910:2.)

Next, the construction requires that the "***amount*** [of effervescent agent] is greater than that ***required*** for disintegration." This construction neither prohibits the effervescent agent(s) from aiding in tablet disintegration, nor requires that the effervescent agent(s) must aid in tablet disintegration. The Khankari patents specifically recognize that in many cases a separate disintegrant should be incorporated in the tablet, and also that the effervescent agents may, in reality, facilitate disintegration. (JTX-2 at 2:41-53, 4:40-51, 5:54-58; JTX-4 at 2:44-56, 4:41-50, 5:51-55.) Indeed, the "short" disintegration time fentanyl tablet exemplified in the Khankari patents includes microcrystalline cellulose, a superdisintegrant. (JTX-2 at 6:11-12; JTX-4 at 6:7-8.) Accordingly, the disintegration aspect of the construction simply requires that the amount of effervescent agent be greater than that required for disintegration, if, for example, there were no separate disintegrant in the tablet. Where the tablet includes an effervescent agent and some other disintegrant—which is the case here—the amount of effervescent agent is necessarily greater than that required for disintegration because a different tablet component is present to ensure disintegration.

Lastly, the construction requires that the *amount* of effervescent agent "does not include the pH-adjusting substance separately claimed." In adopting this construction in the *Watson* case, this Court provided that "[w]hile one compound may both adjust pH and participate in effervescence, only the quantity of effervescent agent above that needed for effervescence may be considered the 'pH adjusting substance.'" 769 F. Supp. 2d at 745. Thus, if the alleged pH

adjusting substance is a carbonate, the amount that is a pH adjusting substance is only the amount that is not needed for effervescence. Again, this portion of the construction does not exclude the pH-adjusting substance and the effervescent agent acting together to increase absorption; indeed, that is the invention of claim 2 (and claims dependent thereon) of the '604 patent, and all the claims of the '590 patent. Rather, there only need be some *amount* of effervescent agent that is not the pH adjusting substance separately claimed.

2. Mylan's ANDA Products Contain "At Least One Compound That Evolves Gas by Means of an Effervescent Reaction"

Mylan does not and cannot dispute that the sodium bicarbonate and citric acid in its ANDA Products constitute effervescent agents under the parties' agreed upon construction; these excipients evolve CO_2 gas by means of an effervescent reaction. (D.I. 149 at 552:3-553:11; D.I. 150 at 908:4-14.) Dr. Olsen presented testing data at trial demonstrating that Mylan's tablets evolve CO_2 gas when exposed to water and artificial saliva, including videos showing the evolution of gas from Mylan's ANDA Products. (D.I. 148 at 359:5-360:15, 361:4-12, 362:3-365:8, 366:5-371:19, 372:18-376:19; D.I. 149 at 552:20-553:11, 687:13-15; PTX-371; PTX-373; PTX-375; PTX-376; PTX-377; PTX-378; PTX-379; PTX-380.) Moreover, the fentanyl examples of the Khankari patents employ citric acid and sodium bicarbonate as effervescent agents. (JTX-2 at 6:1-30; JTX-4 at 5:65-6:26.) Accordingly, the first requirement of the disputed claim element of the Khankari patents is met.

3. The Effervescent Agents in Mylan's ANDA Products Are Present In An Amount Sufficient to Increase the Rate and/or Extent of Fentanyl Absorption Across the Oral Mucosa

The second requirement of the effervescent agent limitation—the absorption element—is also plainly met. A spectrum of data supports Dr. Illum's opinion that the effervescent agents in Mylan's ANDA Products increase the rate and extent of absorption of fentanyl absorbed across

the buccal mucosa. Dr. Illum explained how Mylan's development efforts and clinical data, CIMA'S clinical data, CIMA'S animal data, and *in vitro* data each compel the conclusion that effervescence increases the rate and extent of fentanyl absorption across the oral mucosa.

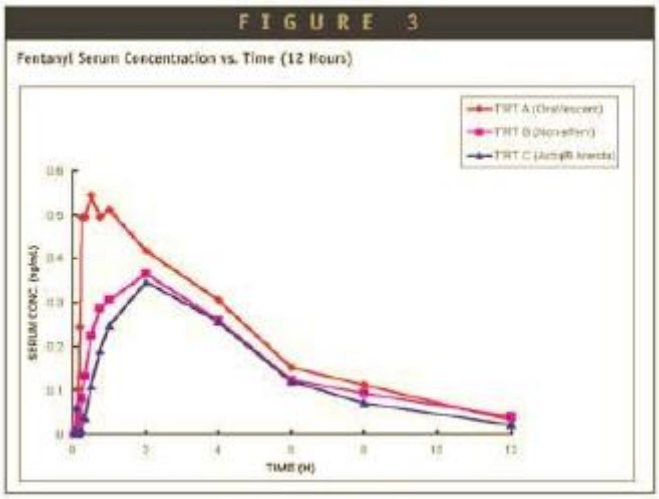
At trial, Mylan tried to downplay the sufficiency of the record evidence because it did not ***all*** result from studies that looked at the role of effervescence completely independent of pH modification. In so doing, Mylan improperly suggests that to establish infringement Cephalon must prove that effervescence improves absorption independent of a pH effect. But, as demonstrated above, that is not what the construed claims require. Moreover, it stands in stark contrast to what Dr. Khankari invented. Effervescence is a pH modifier, as Mylan recognized. There is no reason why the synergistic effects of a pH adjusting substance (sodium carbonate in Mylan's ANDA Products) in addition to effervescence (sodium bicarbonate and citric acid in Mylan's ANDA Products) cannot also be considered to show that the effervescence in Mylan's ANDA Products increases the rate and extent of fentanyl absorption across the oral mucosa.

Each portion of the evidence discussed below shows that the effervescent agents in Mylan's ANDA Products improve absorption of fentanyl across the oral mucosa. Taken together, the evidence is stark and compelling: effervescence improves absorption, exactly as Mylan's scientists already know.

a. CIMA'S First Clinical Study In Ireland Demonstrates that the Effervescent Components in Mylan's ANDA Products Increase Fentanyl Absorption

CIMA'S initial clinical study conducted in Ireland demonstrates that the amount of effervescence in Mylan's ANDA Products increases the rate and extent of fentanyl absorption across the oral mucosa. As discussed above and as depicted below (PTX.266A.5), the results from that study show that a fentanyl buccal tablet formulation containing the same effervescent agents, 21% sodium bicarbonate and 15% citric acid, and the same pH adjusting substance, 10%

sodium carbonate, as Mylan's ANDA Products produced higher blood levels (C_{max}) and a greater extent of fentanyl absorption (AUC) than both a non-effervescent tablet with lactose instead of sodium bicarbonate, citric acid, and sodium carbonate, and Actiq®. (D.I. 149 at 554:1-556:18; PTX-266A.3, .5; DTX-541 at CEP-FEN00150997-998.)



Testing of the two buccal tablets studied in Ireland show that effervescence improves absorption independent of both tablet disintegration and pH. As for disintegration, both tablets "had similar disintegration times (10 minutes) as tested by a specially developed method for buccal tablets." (PTX-266A.3.) Dr. Weiner did not disagree with that point, and Dr. Illum confirmed that the data meant disintegration was controlled for, and thus did not contribute to the absorption differences between the tablets. (D.I. 149 at 555:25-556:18; D.I. 150 at 940:21-941:3.)

As for pH, CIMA'S measurements revealed that the effervescent and non-effervescent formulations had the same *in vitro* pH upon exposure to 5 mL of buffer for 10 minutes, thus confirming that any absorption differences are not attributable to the tablets having different final pH values. (D.I. 149 at 695:25-698:16; D.I. 150 at 898:23-900:15, 941:5-942:1, 943:25-945:6,; PTX-438.3 (reporting average pH values of 6.8 and 7.0 for effervescent and non-effervescent

tablets tested in 5 mL, respectively); DTX-540 at CEP-FEN00050350-51; DTX-21 at CEP-FEN00965583.) While Dr. Weiner took issue with the *in vitro* pH data because CIMA later changed its pH profile method to use less buffer for its registration batches (D.I. 150 at 899:24-900:1, 945:13-946:1; DTX-21 at CEP-FEN00965579), pH testing conducted under the new method drew the same conclusion that "effervescent components and pH modifier contribute to a dynamic change in the microenvironment of the tablet which promotes the formation of ionized and unionized portions of fentanyl in solution." (DTX-21 at CEP-FEN00965581; D.I. 150 at 946:6-949:6.)

Put simply, the Ireland study shows that effervescence increases the rate (C_{max}) and extent (AUC) of buccal fentanyl absorption compared to non-effervescent formulations irrespective of disintegration and final tablet pH. (*See* D.I. 150 at 940:10-20.) That finding is equally applicable to Mylan's ANDA Products because they use the same key ingredients (sodium bicarbonate, citric acid, and sodium carbonate) in the same amounts that were investigated in the Ireland clinical study. (*Compare* PTX-292.1, *with* DTX-199 at CEP-FEN00398374-75, *or* DTX-541 at 150997-998.)

b. Mylan's Data Confirms that the Effervescent Agents In Its Products Increase Fentanyl Absorption

Mylan's development path likewise demonstrates that the amount of effervescence in Mylan's ANDA Products increases the rate and extent of fentanyl absorption across the oral mucosa. As discussed above in section IV.D.2, Mylan investigated several non-effervescent formulations as an alternative to effervescent formulations, but none proved successful. (D.I. 149 at 561:4-565:23, 562:6-17; PTX-188.3.) As Mylan acknowledged, each of its non-effervescent formulations had similar PK profiles, which were each too low to be bioequivalent to Fentora®. (D.I. 149 at 564:8-565:17; PTX-75.4.) But when Mylan chose to mimic the

Fentora® formulation and use sodium bicarbonate, citric acid, and sodium carbonate, Mylan saw "an enormous change" in the resultant PK profiles, which provided absorption even higher than Mylan desired. (D.I. 149 at 565:18-568:8; PTX-75.4.) "The [effervescent] plasma profiles show that you have a Cmax that has increased tremendously and . . . the rate of absorption has changed very much." (D.I. 149 at 568:1-3.) The overall shape of the PK profiles of Mylan's first two effervescent formulations were essentially identical to Fentora®'s PK profile. (*Id.* at 566:23-567:20; PTX-75.4.) Thus, the effect of effervescence, as Mylan demonstrated, was to improve the rate and extent of buccal fentanyl absorption. (D.I. 149 at 570:6-571:5; PTX-75.4, 6.)

Unsurprisingly, Mylan concluded from this data that the characteristics of its effervescent and non-effervescent formulations differed, stating that "effervescence has [a] larger effect on PK than other pH modifiers; pH modification alone and effervescence ***are not equivalent***." (D.I. 149 at 569:24-570:12; PTX-75.4 (emphasis added).) Indeed, Mylan was unable to achieve bioequivalence to Fentora® with pH modification alone. This held true for lot 1000306, which included both acidic and basic pH modifiers and produced a dynamic pH profile (it initially dropped and then raised slowly), and for Mylan's other non-effervescent formulations whose pH profiles showed a higher final pH. (DTX-680 at MYLAN 518098; D.I. 149 at 580:1-582:5, 583:11-584:3.) In short, Mylan found—just as Dr. Khankari's patents describe—that effervescence enhances oral transmucosal drug absorption.

Mylan even understood that one way effervescence increases absorption is through its dynamic effect on the pH of saliva. Mylan's Dr. Kuntz aptly illustrated in a presentation to his boss, Dr. Wargo, how the weakly basic drug, fentanyl, ionizes at a relatively low pH, and converts to its unionized form at a relatively higher pH. He tied those pH-based concepts to effervescence, commenting that both Fentora® and Mylan's effervescent buccal tablets use

effervescence to take advantage of the optimal pH conditions for fentanyl absorption. (D.I. 149 at 558:1-559:22; PTX-115.8.) Mylan's ANDA confirms this, stating that its "formulation uses an effervescent mechanism which is similar to the reference listed drug [Fentora®]." (D.I. 149 at 556:19-557:25; PTX-188.3.)

c. *In Vivo* Dog Data Demonstrates that Effervescence Enhances Fentanyl Absorption

CIMA'S study of effervescent formulations in dogs further demonstrates that effervescence increases fentanyl absorption across the oral mucosa. By way of background, CIMA contracted with Anesta—the competitor company that made Actiq®—to perform an *in vivo* study in dogs measuring the buccal absorption of fentanyl from four tablets manufactured by CIMA. (D.I. 149 at 708:8-13; D.I. 150 at 876:24-877:4, 917:5-10, 959:3-7; PTX-320.1, .6-11.) Two tablets had a short disintegration time, the other two a long disintegration time. And within each set of those tablets, one had both effervescent and pH adjusting components whereas the other did not. The two short disintegrating tablets had 5% crospovidone; the long disintegrating non-effervescent tablet had 2% crospovidone; and the long disintegrating effervescent table had none. (DDX-215.) In addition, two fentanyl solutions were tested. One had a pH of 7, while the other was targeted to have a pH of 8.4 and, as discussed below, reached a pH of 8.05. (D.I. 149 at 587:24-589:4, 702:25-704:21; D.I. 150 at 879:20-880:21, 950:14-951:2; PTX-320.11; DTX-397; DTX-204; DDX-215.)

The objective of the dog study was "to evaluate the hypothesis that effervescence, independent of pH, enhances the permeability of fentanyl through the buccal mucosa." (D.I. 149 at 586:22-587:12; PTX-320.6.) The study was thus ***not*** done to test the dynamic pH mechanism, as Dr. Illum noted, but rather to test other possible mechanisms of effervescence—*e.g.*., those listed elsewhere in the '604 patent. (PTX-320.33; D.I. 149 at 587:16-20, 702:25-704:21; JTX-2

at 2:20-28.)

But even still, the study plainly demonstrated that effervescence enhances absorption. The pharmacokinetic profiles from the study show that, consistent with Dr. Khankari's invention, the long-disintegrating effervescent (LDE) formulation produced the highest fentanyl absorption (top curve) as compared to both the long-disintegrating non-effervescent (LDNE) formulation (bottom curve) and the fentanyl solutions (middle curves). (D.I. 149 at 588:16-589:23, 590:24-591:6, 705:3-22; D.I. 150 at 956:1-; PTX-320.20.)

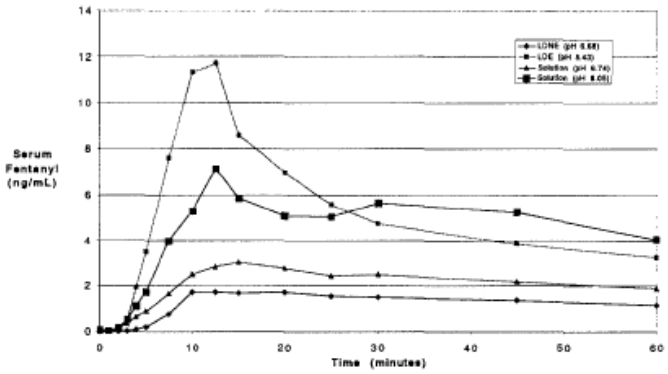


Figure 4. The mean concentration-time profile (n=6) for the formulations administered over 10 minutes.

To compare, the LDE tablet produced a statistically significantly higher mean C_{max} than the LDNE tablet (12.46 ng/mL vs. 1.98 ng/mL) and a greater mean AUC than the LDNE tablet (310.17 min·ng/mL vs. 78.82 min·ng/mL). (D.I. 150 at 955:22-956:23; PTX-320.17.) Likewise, the short-disintegrating effervescent (SDE) tablet produced a higher mean C_{max} than the short-disintegrating non-effervescent (SDNE) tablet (8.57 ng/mL v. 1.51 ng/mL), a shorter mean T_{max} than the SDNE tablet (7.5 min v. 18.33 min), and a greater mean AUC than the SDNE tablet (250.37 min·ng/mL v. 58.96 min·ng/mL). (D.I. 150 at 952:21-955:21; PTX-320.15; PTX-320.16.) As noted, both short-disintegrating tablets contained 5% superdisintegrant. (DDX-215.)

Thus, the Anesta dog study shows that effervescence increases the rate (as measured by C_{max} and T_{max}) and extent (as measured by AUC and C_{max}) of buccal fentanyl absorption compared to a non-effervescent tablet. (D.I. 149 at 588:16-593:10; D.I. 150 at 952:21-955:7.) An additional, remarkable output of the dog study is that the LDE tablet—which had to begin disintegrating for fentanyl to dissolve into solution—produced a faster rate of absorption (T_{max} of 11.67 min) than the pre-made fentanyl solutions (T_{max} of 17.08 and 15.00 min), which did not have any disintegration requirements. (D.I. 149 at 590:9-23; D.I. 150 at 956:24-957:11; PTX-320.17-18.) To illustrate, the C_{max} of the LDE tablet was 12.46 ng/mL compared to 8.04 ng/mL for the pH 8 solution and 3.32 ng/mL for the pH 7 solution. (D.I. 150 at 957:12-958:8; PTX-320.3 (tbl.1a).) This is true even for the pH 8 solution that was not a static pH solution (like the pH 7 solution), but was Anesta's attempt to mimic the dynamic pH change of the LDE tablet by increasing the solution pH from 7.0 to 8.05 by adding aliquots of pH 9.4 buffer. (D.I. 149 at 589:20-590:23; PTX-320.9, 11.)

Given that CIMA'S SDE and LDE tablets posed competitive risks to Anesta's Actiq®, it is not surprising that the Anesta reviewers criticized the results of the dog study. In their eyes, the study did "not support the hypothesis that effervescence enhances fentanyl absorption through the buccal mucosa, as pH was not constant during the administration of the fentanyl tablets." (PTX-320.2.) Of course, effervescence is predominantly a pH effect, so Anesta's criticism is essentially a circular one. But, even accepted at face value, as Dr. Illum explained, there was a poor correlation between pH and absorption in the dog study, so the data does not support Anesta's or Dr. Weiner's conclusions that saliva pH significantly affects AUC and effervescence does not. (D.I. 149 at 705:23-708-13; PTX-320.19 at figs. 2&3, PTX-320.32 (cmt. 8).)

The conclusions drawn by CIMA scientists better characterize the dog study data. CIMA

concluded that Anesta wholly ignored that "pH effects only partially explain the better absorption of the drug, and some other factor must explain the remainder of the enhanced absorption." (D.I. 149 at 707:23-708:7; PTX-320.32 (cmt. 8).) CIMA also explained that Anesta's theory that a higher pH alone caused improved absorption could not work because, consistent with Dr. Khankari's explanation, higher pH values do not favor fentanyl dissolution, and thus "have a negative influence on the overall dissolution-absorption process. Thus, higher pH alone cannot fully explain the improved absorption of the drug that was seen in this study." (D.I. 150 at 962:10-963:6; PTX-320.32 (cmt. 9).) Instead, effervescence plays a dynamic role in altering the pH of saliva, first favoring fentanyl dissolution with an initial pH decrease and then favoring fentanyl absorption with a gradual pH increase. (PTX-320.32.) It was "erroneous [for Anesta] to state that effervescence does not enhance fentanyl permeability when effervescence is the mechanism whereby pH is continually changing." (D.I. 150 at 963:16-964:11; PTX-320.33 (cmt. 11).) In other words, effervescence produces a dynamic pH and a dynamic pH enhances absorption.

d. *In Vitro* Study on Human Buccal Cells Shows that Effervescence Improves Absorption

In vitro data from a study on human buccal cells further confirms that effervescence improves absorption as compared to pH modification alone. In that study, which was commissioned by CIMA and performed by Absorption Systems, the rate of fentanyl permeating across the buccal cell membrane—from the donor chamber to the receiver chamber—was measured from six fentanyl-containing tablets.[6] (D.I. 149 at 666:23-669:11; DTX-57 at CEP-

[6] The six formulations studied were labeled effervescence (containing effervescent agents sodium bicarbonate and citric acid, and pH adjusting substance sodium carbonate), one-half effervescence (containing one half the concentration of the same ingredients as the effervescent formulation), no sodium carbonate (containing citric acid and sodium bicarbonate), non-effervescent, citric acid only, and sodium carbonate only. (D.I. 149 at 666:23-669:11.)

FEN000471813.) The tablets were placed on the surface of buccal cell tissue and buffered solution was added every minute for four minutes. The formulations and solution were then mixed for one minute. (DTX-57 at CEP-FEN0471813.) After those five minutes, samples of the solution were taken from the receiver chamber to measure the rate of permeability (P_{app})—a measure of rate and extent. (*Id.*; D.I. 149 at 709:24-711:5; D.I. 150 at 965:4-11; 966:11-23.)

Accordingly, "time zero" in the experiments was, in reality, five minutes after the tablet was exposed to the mucosa. As Dr. Illum explained, those five minutes matter—as was evident in the video presentations, effervescence occurs immediately upon introduction of saliva to an effervescent pill, and the dynamic pH mechanism begins right away. (D.I. 148 at 374:5-375:19; D.I. 149 at 690:15-24, 710:9-713:17; DTX-57 at CEP-FEN01146466 (fig. 6); DTX-379; DTX-380.) Data from a test that largely discounts those first five minutes should be viewed with skepticism. (D.I. 149 at 710:9-713:17.)

Nonetheless, these *in vitro* experiments plainly demonstrate that effervescence enhances absorption and highlight the synergies available when using both effervescence and a separate pH adjustor. In the study, both effervescent and half-effervescent tablets (each of which contained citric acid, sodium bicarbonate and sodium carbonate) had far greater P_{app} values than the pH only (sodium carbonate only) formulation, showing that the combination of effervescence and pH adjustor is far better than pH adjustor alone, just as Mylan learned. (D.I. 149 at 713:18-714:21; D.I. 150 at 964:13-966:16; DTX-57 at CEP-FEN01146467; DTX-56 at CEP-FEN00471819.) In addition to showing the synergy, the comparison of the effervescent and half effervescent tablets shows that a larger amount of effervescence improves absorption more than a smaller amount of effervescence. (D.I. 149 at 712:4-21, 715:24-716:5; DTX-57 at CEP-FEN01146467; DTX-56 at CEP-FEN00471819.)

Indeed, the study's authors concluded that "[e]ffervescent mediated enhancement of buccal delivery of drugs represents an attractive option for drugs subject to first-pass metabolism." (D.I. 149 at 716:6-23; DTX-57 at CEP-FEN01146444.) And while Mylan's expert Dr. Weiner fixated at trial on the P_{app} values for the effervescence only formulation that were comparable to the pH only formulation, he did not look at the data behind those P_{app} values—*i.e.*, the actual concentrations of fentanyl measured in the receiver chamber. (D.I. 150 at 967:21-968:3.) At "time zero" in the experiment—which was actually 5 minutes ***after*** the tablets were introduced to the donor chamber—the ***only*** tablets for which fentanyl had permeated the membrane and entered the receiver chamber were the tablets that contained effervescent agents. (D.I. 150 at 967:21-973:3; DTX-56 at CEP-FEN00471828-829.) Not even the fentanyl solutions that contained pre-dissolved fentanyl permeated the membrane at "time zero." (*Id.*) Effervescence—and effervescence alone—enhanced absorption of fentanyl in the first five minutes of the experiment.

All these data are again consistent with the Khankari patents' teaching that effervescence increases oral transmucosal absorption, whether by itself or in synergy with a pH adjustor. It is especially striking that this study confirms the criticality of the first five minutes of the effervescence cycle—data poorly reflected in the P_{app} table on which Mylan's expert so heavily relied. Effervescence enhances absorption.

4. The Effervescent Agent In Mylan's ANDA Products Is Present In An Amount That Is Greater Than That Required for Disintegration

Not only do the effervescent agents in Mylan's tablets increase the rate and extent of fentanyl absorption across the oral mucosa, those effervescent agents are also present in an amount greater than is required to disintegrate Mylan's tablets. In fact, none of the effervescent agents in Mylan's tablets is required for tablet disintegration because Mylan's tablets contain a

specific excipient—superdisintegrant SSG at 4% by weight—for disintegration. 4% SSG is more than sufficient to disintegrate Mylan's tablets apart from any disintegration effect effervescence may impart. (D.I. 149 at 571:9-572:13, 578:1-5; PTX-75.3.) Mylan did not present any evidence at trial that the 4% SSG in its tablets does not adequately disintegrate its tablets. In fact, Mylan told FDA that SSG is the only "Disintegrant" in its ANDA Products. (PTX-188.1, 3.) And Mylan's ANDA Products use even ***more*** SSG (4%) than Fentora® (3%). (D.I. 149 at 577:13-25; PTX-264.18.) Simply put, Mylan's ANDA Products do not require any amount of effervescent agent for tablet disintegration, as Mylan well knows, having itself used superdisintegrants for orally disintegrating tablets that disintegrate within 30 seconds and have no effervescence. (D.I. 148 at 384:15-385:20.)

CIMA'S clinical study in Ireland demonstrates that no amount of effervescent agent is required for disintegration when the tablets include sufficient superdisintegrant, as Mylan's ANDA Products do. The effervescent and non-effervescent Khankari prototype formulations studied in Ireland both contained 3% crospovidone, a superdisintegrant like SSG. (DTX-199 at CEP-FEN00398374-75; D.I. 150 at 939:23-940:9.) Those tablets had "similar disintegration times," demonstrating that 3% by weight of a superdisintegrant alone sufficiently disintegrated the tablets without any effervescent "assistance," as admitted by Dr. Weiner. (PTX-266A.3; D.I. 150 at 940:17-941:3.) In other words, no amount of effervescent agent is ***required*** to disintegrate a tablet that already contains enough superdisintegrant for disintegration.

Mylan's development work further underscores the conclusion that the effervescent agents in its tablets are present in an amount greater than required for disintegration. Mylan's first non-effervescent formulation, lot 1000306, contained 5% SSG and Mylan did not report any disintegration problems with those tablets. Curiously, Mylan claims that the same 5% SSG in its

two other non-effervescent formulations failed to disintegrate those tablets, but, as demonstrated above, *in vivo*, they minimally differed from Fentora®. (*See* Section IV.D.4.) But even if there were some problem with these two formulations, some tablet component other than SSG must have been the source of the alleged problem since 5% SSG adequately disintegrated lot 1000306, and 4% SSG adequately disintegrates Mylan's proposed tablets, according to its ANDA. Any other component that might have been a problem in the second two non-effervescent formulations was eliminated from Mylan's effervescent formulations. (*Compare* DTX-680 at MYLAN 518089, *with id.* at MYLAN 518090.)

Any suggestion by Mylan that Cephalon must show that effervescence does ***not*** participate in tablet disintegration whatsoever to prove infringement is wrong. The agreed-upon claim construction does not require such a showing. The construction requires only that the "amount" of effervescent agent be "greater than that required for disintegration." The construction therefore allows the effervescent agent to facilitate disintegration at some level. To meet this part of the construction, there only need be more effervescent agent than what would be needed for disintegration only. This element is easily met because there is sufficient SSG in Mylan's tablets to disintegrate the tablets and the effervescent agents improve absorption of fentanyl across the oral mucosa.

Moreover, the Khankari patents recognize that although effervescent components may contribute to tablet disintegration, non-effervescent disintegrants are preferable. (JTX-2 at 2:41-53, 4:41-51; JTX-4 at 2:44-56, 4:41-51.) In other words, if an accused formulation did ***not*** contain a separate non-effervescent disintegrant, some larger amount of effervescent agent might be required to meet this claim element. In that case, one might have to parse out the amounts of effervescent agent contributing to disintegration and then to increased absorption to determine

infringement. But no such undertaking is necessary here. Because Mylan's formulation contains a separate disintegrant that causes tablet disintegration, any amount of effervescent agent satisfies this "greater-than-required-for-disintegration" requirement of the claim limitation. This is especially true for Mylan's formulation, which contains 4% SSG—a larger amount of superdisintegrant than Fentora®.

In sum, because of the presence of SSG, the effervescent agents in Mylan's tablets are not required for disintegration. The amount of effervescent agent in Mylan's tablets is greater than is required for tablet disintegration, and this third requirement of the disputed claim element of the Khankari patents is literally met.

5. The Amount of Effervescent Agents in Mylan's ANDA Products Does Not Include the pH-Adjusting Substance—the Sodium Carbonate—Separately Claimed

The last requirement of the parties' agreed upon construction requires that the "amount" of effervescent agent that is present to enhance absorption does "not include the pH-adjusting substance separately claimed," which is the sodium carbonate in Mylan's ANDA Products. Because the amount of effervescent agents (sodium bicarbonate and citric acid) is unquestionably in an amount that does not include the sodium carbonate, a separate excipient in Mylan's ANDA Products, this part of the claim construction is met.

As explained by Dr. Illum, sodium carbonate is a well-known basic pH adjusting substance, and it is included in Mylan's formulation for that purpose. (D.I. 149 at 578:6-579:13, 608:11-609:9.) Mylan's tablets contain sodium bicarbonate and citric acid in amounts that will cause the sodium bicarbonate to fully react to produce effervescence. (*Id.* at 609:19-23.) The separate pH-adjusting substance, sodium carbonate, modifies the pH of saliva. (*Id.* at 612:4-7.) Indeed, in the context of the Moe '92,832 patent, Mylan admits that the sodium carbonate is a pH-adjusting substance, and, presumably, does not dispute it for the Khankari patents. (*See* D.I.

144.) The only disputed factual issue is whether some small portion of the sodium carbonate will also effervesce. But whether that is true is not relevant to the Khankari patents. While some excess sodium carbonate may react with a small amount of citric acid, that reaction is much less preferable than the reaction between sodium bicarbonate and citric acid to evolve CO_2 gas. (D.I. 149 at 609:23-612:3.) The sodium bicarbonate and citric acid in Mylan's tablets are effervescent agents and, at a minimum, the great majority of sodium carbonate in Mylan's tablets is a separate pH adjusting substance. (*Id.*)

Thus, Mylan's sodium carbonate satisfies the last requirement of the disputed claim element, which simply requires separate amounts of effervescent agent and pH adjusting substance. *See Watson*, 769 F. Supp. 2d at 745 ("While one compound may both adjust pH and participate in effervescence, only the quantity of effervescent agent above that needed for effervescence may be considered the 'pH adjusting substance.'"); *see also* D.I. 117. And while the parties have agreed to apply the claim construction from the *Watson* case, the circumstances here are very different. In *Watson*, Cephalon was attempting to prove that one compound—potassium bicarbonate—served both the function of effervescent agent (reacting with mannitol), as well as adjusting pH. 769 F. Supp. 2d at 745, 747. Here, of course, Mylan's tablets contain 15% citric acid by weight, 21% sodium bicarbonate by weight, and 10% sodium carbonate by weight, just like Fentora® and the fentanyl examples in the Khankari patents. (D.I. 149 at 542:5-23, 543:19-544:21; PTX-292.4-5; PTX-264.20; JTX-2 at 6:1-30.)

As explained above, this portion of the agreed-upon claim construction does not mean that the separately claimed pH adjustor cannot work with the effervescent agent to enhance the absorption. Indeed, the implications by Mylan to the contrary at trial run counter to the express disclosure of the Khankari patents, which describe the two working together. (JTX-2 at 3:15-

43.) As demonstrated above, the data in this case show effervescence improves absorption, in part, by causing a dynamic pH shift in saliva, which takes advantage of fentanyl's propensity to dissolve at a lower pH and be absorbed at a higher pH. Because the efficiency of drug dissolution and absorption is intimately tied to pH, the effervescent technology improves absorption by manipulating pH to promote both drug dissolution and absorption—the pharmaceutical "holy grail." (D.I. 147 at 162:3-163:6.) And, as the patents state, further pH manipulation with the pH adjustor can help optimize this effect. (JTX-2 at 3:15-43.)

This is the same point made by Dr. Kuntz in his presentations about Mylan's buccal products: "effervescence has larger effect on pK than other pH modifiers; pH modification alone and effervescence are not equivalent." (DTX-680 at MYLAN at 518091.) As recognized by Dr. Kuntz, effervescence is fundamentally a pH modifier. And its primary advantage is that it works better than other, traditional pH modifiers, including by working synergistically with them to both enhance solubility and absorption in a dynamic manner.

But the dynamic pH effect—either alone or in combination with a pH adjusting substance—is not the only way that effervescence increases absorption. In her testimony, Dr. Illum identified mechanisms separate from the dynamic pH effect that also explain how effervescence improves absorption. (D.I. 149 at 581:8-583:10.) She explained that the literature reports that CO_2 bubbles may disturb the surface layer of the mucosal membrane, and in doing so aligns the molecules in the membrane to make them more lipophilic. (*Id.*) Since unionized fentanyl is very lipophilic, it more readily interacts with a mucosal membrane that is more lipophilic. (*Id.*) These additional mechanisms likely explain the additional absorption observed, for example, in the Anesta dog study. (PTX-320.32 (cmt. 8).)

Dr. Illum also explained how the pH profiles of Mylan's development formulations show

that effervescence improves absorption in part through other mechanisms. In a low volume (2 mL) pH study, Mylan's non-effervescent lot 1000306 produced a pH profile characterized by an initial decrease from about 6.5 to 4, followed by a slow rise in pH. (D.I. 149 at 579:23-581:7; DTX-680 at MYLAN 518098.) While this non-effervescent formulation produced a dynamic pH, it was not bioequivalent to Fentora®. (D.I. 149 at 581:8-582:5; DTX-680 at MYLAN 518098.) These data demonstrate that there are "other reasons why we see a much higher absorption of the fentanyl" apart from the dynamic pH effect. (D.I. 149 at 581:8-582:5.) For example, the bubbles generated by the effervescence reaction may disturb the surface layer of the mucosal membrane, making it more susceptible to pH changes, or the CO_2 can align the molecules in the buccal membrane making it more lipophilic, which attracts lipophilic fentanyl. (*Id.* at 582:10-583:10.)

C. Mylan Indirectly Infringes the Asserted Claims of the Khankari Patents

Having demonstrated that Mylan's ANDA Products meet the contested effervescent agent limitation in the Khankari patents, it is straightforward that Mylan's ANDA Products and the use of those products literally meet all the remaining elements of asserted claims 1, 2, 3, 11, and 12 of the '604 patent and claims 1, 2, and 7 of the '590 patent, and thus infringe those claims under the doctrines of induced infringement and contributory infringement.

1. Mylan Indirectly Infringes Claim 1 of the '604 Patent

Claim 1 of the '604 patent reads as follows, with the disputed element addressed above highlighted in bold (JTX-2):

> A method of administering at least one systemically distributable pharmaceutical agent across the oral mucosa comprising:
> a) providing a solid oral dosage form including a pharmaceutically effective amount of an orally administerable medicament;
> ***and at least one effervescent agent in an amount sufficient to increase absorption of said orally administerable medicament across the oral mucosa***;

wherein said orally administerable medicament is not substantially encompassed by or dispersed in a material that prevents absorption of said medicament across the oral mucosa;
b) placing said solid oral dosage form in the mouth of a patient so that saliva in said patient's mouth activates said at lea[s]t one effervescent agent in said tablet; and
c) holding said solid oral dosage form and the dissolving contents of said solid oral dosage form in the mouth of a patient whereby said at least one effervescent agent promotes absorption of said orally administerable medicament across the oral mucosa.

The first element of claim 1, "a method of administering at least one systemically distributable pharmaceutical agent across the oral mucosa" is met by the intended use of Mylan's buccal tablets in treating breakthrough cancer pain. (D.I. 149 at 546:18-547:9.) Mylan's label instructs patients to place the fentanyl citrate buccal tablet in the buccal cavity, meaning that Mylan intends for fentanyl—which is a systemically distributable pharmaceutical agent—to be administered across a patient's oral mucosa. (*Id.* at 547:10-548:7; PTX-249.1, 7, 36.)

As to the second element of claim 1, there is no dispute that Mylan's fentanyl buccal tablets are a solid oral dosage form—tablets—including a pharmaceutically effective amount of an orally administerable medicament—fentanyl. (D.I. 149 at 546:12-547:20.) Mylan's ANDA expressly states that its proposed products are tablets, which are solid oral dosage forms. (*Id.* at 547:10-17, 548:17-549:2; PTX-249.1.) And because Mylan's ANDA claims bioequivalence to FENTORA®, Mylan's Products contain a pharmaceutically effective amount of fentanyl citrate, just like Fentora®. (D.I. 149 at 544:22-546:11, 549:14-550:14; PTX-290.)

There is however, a minor dispute—dependent on claim construction—about who will perform the "providing" aspect of second element of claim 2. This claim language does not require an external "provider" as Mylan has argued (though not, apparently at trial);[7] rather, a

[7] As Mylan has never explained the so-called "joint infringement problem" created by its claim construction position, Cephalon will address that issue if Mylan raises it in response. All Cephalon can say now is that it appears to have been waived by Mylan at trial.

patient can provide a tablet to herself, as the cases show. (*See* D.I. 132 at 2-4; D.I. 136 at 1-2.) *Meyer Intellectual Props. Ltd. v. Bodum, Inc.*, 690 F.3d 1354, 1369 (Fed. Cir. 2012) (construing "providing" in a method claim and finding that anyone—the product's seller or product end user—can satisfy that providing step). Accordingly, as Dr. Illum explained, patients can provide Mylan's tablets to themselves, thereby satisfying this element under Cephalon proposed construction. (D.I. 149 at 547:15-549:5.)

The third element of claim 1—the disputed effervescent agent limitation—is addressed in detail above. Mylan's product meets that limitation for the reasons stated above.

As to the fourth element of claim 1, there is also no dispute that the fentanyl in Mylan's ANDA Products is not substantially encompassed by or dispersed in a material that prevents the absorption of fentanyl across the oral mucosa. (*Id.* at 594:3-595:1; PTX-293.4-5.)

As to the fifth element of claim 1, the "placing" limitation, Mylan's labeling undisputedly instructs patients to place the Mylan buccal tablet in their mouth. (D.I. 149 at 595:2-19; PTX-249.1, 7, 36.) Further, as demonstrated by Dr. Olsen's data, the effervescent agents in Mylan's tablets—sodium bicarbonate and citric acid—are activated upon contact with saliva; they begin to evolve gas. (D.I. 149 at 595:20-596:7; PTX-378 at 3; PTX-380.)

Lastly, as to the sixth element of claim 1, the "holding" limitation, Mylan's labeling undisputedly instructs patients to hold the Mylan buccal tablet and its dissolving contents in their mouth. (D.I. 149 at 596:8-597:9; PTX-249.1, 7, 36.) And, as described above, doing so will result in effervescence promoting absorption of fentanyl across the buccal mucosa.

Accordingly, users of Mylan's product will directly infringe claim 1 of the '604 patent. Because Mylan will encourage that use through its product labeling and sale of its generic tablets, Mylan will induce infringement. *AstraZeneca LP v. Apotex, Inc.*, 633 F.3d 1042, 1056-

60 (Fed. Cir. 2010). Moreover, because there is no substantial non-infringing use of Mylan's tablets, Mylan will also contribute to that infringement. *Eli Lilly & Co. v. Actavis Elizabeth LLC*, 435 Fed. App'x 917, 927 (Fed. Cir. 2011) (generic defendants liable for contributory infringement where the FDA-authorized use was patented because "defendants are restricted from selling a federally regulated drug for unapproved uses").

2. Mylan Indirectly Infringes Claims 2, 3, 11 and 12 of the '604 Patent

The additional element that claim 2 adds to independent claim 1—at least one pH adjusting substance—is undisputedly met because Mylan's tablets contain sodium carbonate, which acts as a pH adjusting substance. (D.I. 149 at 597:22-598:24; D.I. 150 at 908:4-14; PTX-293.4-5; JTX-2 at 7:32-35.) Accordingly, Mylan's Products and their intended use will infringe claim 2 of the '604 patent for the same reasons as they infringe claim 1.

Claim 3 limits claim 1 to buccal administration as follows: "step (c) includes holding said solid oral dosage form and the dissolving contents of said solid oral dosage form in said mouth adjacent a cheek for buccal administration." (JTX-2 at 7:36-41.) Mylan does not dispute that this claim element is met, nor can it, since its tablets are buccal tablets that "are intended for buccal mucosal administration," and because Mylan's labeling clearly instructs patients to "place a fentanyl buccal tablet in your mouth above a rear molar tooth between the upper cheek and gum and leave in place until the tablet is dissolved." (D.I. 149 at 598:25-599:22; D.I. 150 at 908:4-14; PTX-249.17, 36.) Mylan infringes claim 3 of the '604 patent.

Claim 11 requires that "said at least one effervescent agent is present in an amount between about 30% by weight and 80% by weight." (JTX-2 at 8:37-40.) Mylan's tablets contain 36% effervescent agent (21% sodium bicarbonate and 15% citric acid) by weight. (PTX-188.1-02; D.I. 149 at 599:23-600:10.) Mylan infringes claim 11 of the '604 patent.

Claim 12 requires that "said at least one effervescent agent is present in an amount

sufficient to evolve a gas in an amount between about 5 cm^3 to about 30 cm^3."[8] (JTX-2 at 8:41-45.) Mylan's 200, 300, 400, 600, and 800 mcg tablets meet this limitation because Dr. Olsen's experiments measured around 8 cm^3 of CO_2 gas evolved from Mylan's 400 mcg tablets upon exposure to water and artificial saliva, and the 200, 300, 600, and 800 mcg tablets contain the same effervescent components in the same amounts as the 400 mcg tablet. (D.I. 148 at 371:2-19; D.I. 149 at 600:11-14; PTX-378.) As Dr. Illum explained, it is unclear whether the 100 mcg tablet will meet this limitation. Accordingly, Mylan infringes claim 12 of the '604 patent, except for its 100 mcg tablet.

3. Mylan Indirectly Infringes Claim 1 of the '590 Patent

To establish Mylan's infringement of claim 1 of the '590 patent, Cephalon must prove by a preponderance of the evidence that Mylan will actively induce someone to perform, or contribute to the performance of, the following elements of the method of claim 1 (JTX-4):

> A method of administration of fentanyl to a mammal across the oral mucosa thereof, said method comprising;
> providing a solid oral dosage form comprising fentanyl or a pharmaceutically acceptable salt thereof
> and at least one saliva activated effervescent agent
> in an amount sufficient to increase absorption of said fentanyl or pharmaceutically acceptable salt thereof across the oral mucosa,
> at least one pH adjusting substance,
> and wherein said amount of said at least one effervescent agent is between about 5% by weight and about 80% by weight; and
> buccally, sublingually or gingivally administrating said solid oral dosage form to said mammal.

The trial evidence demonstrates that Mylan, through its labeling, instructs patients to perform each element of this claimed method, and that Mylan intends for patients to follow the instructions in its labeling. Moreover, there are no other proposed uses for Mylan's tablets other

[8] Claim 12 includes a typo; it recites "cm" (a unit of length) instead of "cm^3" (a unit of volume). The parties have agreed that "cm" should be construed as "cm^3." (D.I. 117 at 3.)

than what is described in Mylan's labeling.

As Dr. Illum explained at trial, there are four differences between claim 1 of the '604 patent and claim 1 of the '590 patent. Claim 1 of the '590 patent requires: (1) delivering fentanyl; (2) at least one pH adjusting substance; (3) at least one effervescent agent present in an amount between about 5% by weight and about 80% by weight; and (4) buccally, sublingually or gingivally administering the solid oral dosage form to a mammal. (D.I. 149 at 601:15-602:8.)

The evidence that Dr. Illum relied upon to establish infringement of claims 1, 2, 3, and 11 of the '604 patent equally establish that claim 1 of the '590 patent is infringed. (*Id.* at 602:9-13.) Accordingly, no additional proofs are required to establish by a preponderance of the evidence that Mylan, through its labeling, instructs patients to perform each element of claim 1 of the '590 patent, and that Mylan intends for patients to follow the instructions in its labeling. Mylan infringes claim 1 of the '590 patent under the law of induced and contributory infringement.

4. Mylan Indirectly Infringes Claims 2 and 7 of the '590 Patent

Claim 2 additionally requires that "said fentanyl or pharmaceutically acceptable salt thereof is administered via a buccal route." (JTX-4 at 7:14-16.) It is undisputed that the fentanyl citrate in Mylan's tablets is intended to be administered via a buccal route; Mylan's labeling clearly states that Mylan's tablets are "intended for buccal mucosal administration." (D.I. 149 at 599:1-22; 602:15-603:3; PTX-249.17.) Mylan infringes claim 2 of the '590 patent.

Claim 7 adds that "said pH adjusting substance is a base." (JTX-4 at 8:8-9.) As discussed above, it is undisputed that a portion of sodium carbonate in Mylan's tablets acts as a pH adjusting substance. (*See* § V.B.5; 598:2-24; PTX-293.4-5.) Sodium carbonate is a base. (D.I. 149 at 598:18-22; 603:4-12.) Mylan infringes claim 7 of the '590 patent.

In sum, because Cephalon has established by a preponderance of the evidence that Mylan's ANDA Products and their use literally meet all of the elements of the asserted claims of

the Khankari patents, the Court should find each of those claims infringed.

D. Mylan Conceded Infringement of the '92,832 Patent

Mylan conceded infringement of asserted claims 1, 3, 4, and 5 of the Moe '92,832 patent on the eve of trial. (D.I. 144.) Independent claim 1 reads as follows (JTX-8):

> A tablet comprising:
> an amount of fentanyl free base or an equivalent amount of salt thereof selected from the group consisting of about 100 micrograms, about 200 micrograms, about 300 micrograms, about 400 micrograms, about 600 micrograms, and about 800 micrograms, calculated as fentanyl free base,
> an effervescent agent comprising a food acid and a bicarbonate in an amount of about 15 to about 60% by weight of said tablet;
> ***a pH adjusting substance comprising a carbonate in an amount of about 0.5 to about 25% by weight of said tablet, wherein said pH adjusting substance is different from the food acid and the bicarbonate in the effervescent agent***;
> a starch glycolate in an amount of about 0.25 to about 20% by weight of said tablet;
> mannitol in an amount of about 10 to about 80% by weight of said tablet;
> said tablet being suitable for delivery of said fentanyl across the oral mucosa of a patient by buccal administration and having a dwell time that is less than about 30 minutes.

Relevant to the '158 patent (and also the Khankari patents), Mylan's concession means that it has admitted that its tablets contain a pH adjusting substance, as indicated by the bolded claim element above, and further, that that pH adjusting substance is sodium carbonate—*i.e.*, it is "different from the food acid" (citric acid) and "bicarbonate" (sodium bicarbonate).

E. Mylan Directly Infringes the Asserted Claims of the Moe '158 Patent

Mylan's ANDA Products also literally meet all the elements of asserted claims 1, 15, 17, 19, and 21 of the Moe '158 patent. The only dispute on infringement of the '158 patent turns on whether Mylan's ANDA Products contain a "pH adjusting substance [that] is not a component of said effervescent material." As the Court is aware, the parties dispute the proper construction of this phrase. Cephalon proposes that this phrase should be given its ordinary meaning, such that the pH adjusting substance is in addition to the effervescent components of the claimed formulation. (D.I. 117 at 4.) In contrast, Mylan seeks a construction that "the pH adjusting

substance is not one of the components used to generate effervescence." (*Id.*) Mylan applies its construction to prohibit ***any*** carbonate source from serving as a pH adjusting substance because carbonates have some propensity to participate in an effervescent reaction. As demonstrated in the *Markman* briefing, Mylan's approach is wrong. But, in any event, sodium carbonate in Mylan's tablets meets this claim element under both parties' constructions.

1. Mylan Directly Infringes Claim 1 of the '158 Patent

Claim 1 of the '158 patent reads as follows, with the contested limitation in bold (JTX-6):

> A dosage form comprising: from about 200 micrograms to about 800 micrograms of fentanyl, a salt form of fentanyl, or combinations thereof, calculated as fentanyl free base;
> an effervescent material in an amount of about 15% to no more than about 60% by weight of the dosage form;
> a pH adjusting substance in an amount of about 0.5 to about 25% by weight of the dosage form, ***wherein said pH adjusting substance is not a component of said effervescent material;***
> mannitol in an amount of between about 10 and about 80% by weight of the dosage form;
> a starch glycolate in an amount of about 0.25 to about 20% by weight of the dosage form;
> wherein said dosage form is suitable for delivery of said fentanyl across the oral mucosa of a patient by buccal, gingival or sublingual administration.

a. Mylan's ANDA Products Contain the Undisputed Elements of Claim 1 of the '158 Patent

Mylan did not contest that its products meet the un-bolded elements of claim 1. For the record, Mylan's ANDA Products are tablets, which are dosage forms, and have strengths from about 200 micrograms to about 800 micrograms of fentanyl, a salt form of fentanyl, or combinations thereof, calculated as fentanyl free base. (PTX-293. 4-5; D.I. 149 at 605:19-606:21.) Mylan's tablets also contain "an effervescent material in an amount of about 15% to no more than about 60% by weight of the dosage form" because they contain 36% by weight effervescent agent (sodium bicarbonate at 21% and citric acid at 15%), which evolves gas. (PTX-293.4-5; D.I. 149 at 606:22-608:10; PTX-378.) Mylan's Products also contain "mannitol in an amount of between about 10 and about 80% by weight of the dosage form," "a starch

glycolate in an amount of about 0.25 to about 20% by weight of the dosage form" and are suitable for delivery of fentanyl across the oral mucosa of a patient by buccal, gingival, or sublingual administration as described above. (D.I. 149 at 612:11-613:16; PTX-293.4-5; PTX-249.36.)

b. Mylan's ANDA Products Contain the Contested pH Adjusting Substance Limitation Under Both Parties' Constructions

Cephalon contends that the disputed claim phrase "pH adjusting substance is not a component of said effervescent material" is understood according to its ordinary meaning—*i.e.*, that the pH adjusting substance is in addition to the components of said effervescent agent. (D.I. 117.) The 10% by weight sodium carbonate in Mylan's ANDA Products is indisputably a "pH adjusting substance in an amount of about 0.5 to about 25% by weight of the dosage form." (D.I. 149 at 609:7-12; PTX-188.1; PTX-292.1-2; PTX-293.4-5.) As described above, sodium carbonate is a basic substance that adjusts pH. (D.I. 149 at 609:7-9.) Mylan has admitted this function by not contesting infringement of the '92,832 patent. Moreover, sodium carbonate is present in Mylan's tablets in addition to the effervescent components, citric acid and sodium bicarbonate—*i.e.*, it is not the same component. This is not the *Watson* case, where Cephalon was attempting to show that the same component—potassium bicarbonate—both adjusted pH and created effervescence. As explained by Dr. Illum, the sodium bicarbonate and the citric acid in Mylan's tablets preferentially react to generate effervescence, and the sodium carbonate in Mylan's tablets would only interact with the citric acid to evolve gas if it first formed sodium bicarbonate as an intermediary. (*Id.* at 609:13-612:10.) The reaction between sodium carbonate and citric acid is thus more complicated than the reaction between sodium bicarbonate and citric acid because the sodium carbonate/citric acid reaction involves two steps, whereas the sodium bicarbonate/citric acid reaction involves only one. (*Id.* at 610:10-612:3.) But whether some

small amount of the sodium carbonate does react is immaterial—some of it does not and thus adjusts pH, as conceded by Mylan for the '92,832 patent. The 10% by weight sodium carbonate in Mylan's ANDA Products meets this limitation under Cephalon's proposed construction. (*Id.* at 608:11-609:12; PTX-188.1; PTX-292.1-2; PTX-293.4-5.)

Likewise, the sodium carbonate in Mylan's ANDA Products meets this limitation under Mylan's proposed construction. (D.I. 149 at 609:13-612:10.) Mylan's proposed construction provides that "the pH adjusting substance is not one of the components used to generate effervescence." (D.I. 117 at 4.) As explained above, sodium carbonate is not one of the components used to generate effervescence in Mylan's ANDA Products. Rather, the sodium bicarbonate and citric acid primarily generate effervescence in Mylan's ANDA Products. Moreover, any sodium carbonate must first convert to sodium bicarbonate to create effervescence, such that any effervescent reaction of the sodium carbonate, is, in fact, sodium bicarbonate reacting. Thus, sodium carbonate itself functions only to adjust pH. Accordingly, sodium carbonate in Mylan's ANDA Products, even if some of it effervesces, is a pH adjusting substance, not an effervescent agent, under Mylan's proposed construction.

2. Mylan Directly Infringes Claims 15, 17, 19, and 21 of the '158 Patent

Claims 15, 17, 19, and 21 each depend from claim 1. As demonstrated above, each element of claim 1 is satisfied. Dependent claims 15, 17, 19, and 21 each contain an additional element specifying the amount of fentanyl free base (200, 400, 600, and 800 micrograms, respectively), which are also satisfied. Mylan's ANDA tablets contain 200 micrograms of fentanyl free base as required by claim 15, 400 micrograms of fentanyl free base as required by claim 17, 600 micrograms of fentanyl free base as required by claim 19, and 800 micrograms of fentanyl free base as required by claim 21. (D.I. 149 at 613:18-614:16; PTX-293.4-5.) Mylan is therefore liable for directly infringing the asserted claims of the Moe '158 patent.

F. Mylan Indirectly Infringes the Asserted Claims of the Moe Patents

Just as Mylan infringes the '92,832 and '158 patents, users of Mylan's ANDA Products will directly infringe claims 1, 15, 17, 19, and 21 of the '158 patent. Because Mylan will encourage that use through its product labeling and sale of its generic tablets, Mylan will induce that infringement. *AstraZeneca*, 633 F.3d at 1056-60. And because there is no substantial non-infringing use of Mylan's tablets, Mylan will also contribute to that infringement under the standards of the Federal Circuit. *Eli Lilly & Co.*, 435 Fed. App'x at 927.

VI. CONCLUSION

For all the above reasons, the Court should enter judgment that Mylan infringes the asserted claims of the Khankari and Moe patents, order the approval date of Mylan's ANDA to be a date no earlier than patent expiration, and permanently enjoin the commercial use, manufacture, and sale of Mylan's ANDA Products. *See* 35 U.S.C §§ 271(e)(4)(a) and (b).

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